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THE MECHANISM OF SHOCK FROM BURNS AND TRAUMA TRACED WITH RADIOSODIUM

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IN studies of shock emphasis has recently shifted from the plasma proteins and other colloids to the electrolytes. Rosenthal demonstrated that in standardized shock from burns or trauma sodium salts in isotonic solution are as effective as equal volumes of serum and showed that "the curative effects of serum are due to its electrolyte content" (20). Clinical studies in shock caused by extensive thermal burns demonstrated the therapeutic efficacy of large doses of sodium salts in isotonic solution and led to the discovery of an unexpectedly large sodium retention (7).

These investigations pointed to the existence of a heretofore unrecognized and possibly fundamental derangement in shock: redistribution of sodium. Accordingly, radioactive sodium (Na^{24})[1] was used to explore whatever changes might occur after shock from burns or trauma.

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[1]The sodium isotope used in these experiments was prepared in the Radiation Laboratories of Columbia University and was kindly supplied by Dr. John R. Dunning. In accordance with conventional usage (21) the less cumbersome term radiosodium will be used hereafter to denote Na^{24}.

PROCEDURE

Two types of experiments were conducted, the technique of Rosenthal being used for production of standardized shock from burns and from trauma (20). In one type, animals were prepared with radiosodium given in isotonic sodium chloride solution so that the body sodium was in equilibrium and "tagged" with the isotope. Shock was produced 20 hours later and the concentration of radiosodium in the tissues and organs was determined in the animals during shock but not *in extremis*. In a second type of experiment, shock was produced first and the animals were then treated with isotonic saline containing some radiosodium. About 20 hours later, upon recovery from potentially fatal shock (as judged by death of untreated controls), the concentration of radiosodium was determined[2] in tissues and organs. The water content of all tissues sampled was also measured by drying the tissues at 110 degrees C. for 18 to 24 hours. Similar analyses were performed in parallel control animals which had not been injured but had received equal doses of radioactive sodium.

Mice were used for these reasons: the burns produced by Rosenthal's technique are uniformly fatal

[2]The tissues were homogenized by wet ashing and radioactivity was measured with the Geiger-Muller counter. The procedure has been described in detail (15).

in untreated animals (94.6% mortality in 221 controls) and treatment with isotonic solutions of sodium salts is uniformly effective (6% mortality in 708 animals treated with 2.2 to 3.0 c.c. within 5 hours). Shock following application of tourniquets to both hind legs and release after 2 hours is also uniformly fatal (95.3% mortality in 127 controls). Therapy with isotonic solutions of sodium salts (or a protein-free ultrafiltrate of mouse serum) is uniformly effective—85% to 91% survived after the second injection in 200 mice (20). In a single experiment in this laboratory with 100 mice, results similar to those of Rosenthal were obtained. When other animals are used, e.g. dogs, tourniquets must be applied for 5 to 10 hours and the occurrence of infection in the occluded extremities has complicated the "shock" that results (2, 19).

RESULTS

The tissue analyses and plasma values are shown in Tables I and II. The radioactivity values are expressed as percentage of the dose injected per gram of fresh tissue. Thus if 1000 counts per minute of radioactivity (above background) were injected into a mouse and analysis of 1 gram of its tissue showed 10 counts per minute (above background), the activity of the tissue would be 1 per cent of the dose injected. The values for the extremity tissues are listed separately for hind legs and fore legs in all burn experiments in which only the hind legs were burned; also in the experiments on traumatic shock in which tourniquets were applied to the hind legs only.

It is immediately apparent from Tables I and II that the concentration of radiosodium in the skin and muscles of the injured extremities was much greater than the concentrations in similar tissues in the uninjured extremities of the same animal or in normal control animals. There was also a less striking gain in water content in the tissues of the injured hind legs.

The studies of Gamble; Hastings and Eichelberger; Manery and Hastings; Manery and Bale; Peters; and Harrison, Darrow, and Yannet have shown that most of the body sodium (except some in bone) is in the extracellular phase, i.e. in the plasma and interstitial fluid. (The interstitial fluid is essentially an ultrafiltrate of plasma in equilibrium with plasma and containing little protein but nearly as much sodium.) Obviously the influx of plasma or interstitial fluid into tissues causing a gain in water content (edema) will also increase the sodium content of the tissues. Accordingly the analytical values for radiosodium were examined in relation to the movement of these fluids and water. This was done by attempting to ascertain the distribution of sodium and water in the extracellular and intracellular phases of tissues by the formulas of Hastings and Eichelberger. The analytical values for radiosodium were utilized instead of gravimetric analyses by appropriate substitutions. Analogous data for normal animals have been reported by Manery and Bale.

The values for extracellular fluid are obtained by the following calculation[1]:

$$\text{Extracellular water, grams per kgm. (or "sodium space" in injured tissues)} = \frac{\text{Tissue radioactivity (\% dose per gram)}}{\text{Plasma radioactivity (\% dose per gram)}} \times \frac{0.93}{0.95} \times 1000$$

In regions where the antisodium barrier may have been demolished, the sodium concentration in the tissue fluid is unknown; the term "sodium space" is used, therefore, to denote the volume of fluid which would contain all the sodium present in the tissue in a concentration equal to the plasma sodium concentration.

An approximation of intracellular water was obtained by subtracting the above value for sodium space from the total water content. These data are shown in Tables I and II. Figure 1, a and b, show the solids and extracellular and intracellular phases computed for muscle.

The calculation shows a great increase in the volume of "sodium space" in injured tissues and that this increase is far too large to represent a commensurate increase in the volume of extracellular fluid. Thus in some instances the intracellular phase by this calculation would appear to have vanished. It is apparent that the tissues have gained more sodium than water; that the normal sodium space (i.e. extracellular sodium) was infiltrated into the intracellular compartment indicating some demolition of the antisodium barrier. Thus in normal tissues the extracellular phase averaged 200 grams per kilogram and the

[1]This computation has the additional advantage of giving a value for sodium content which is independent of variations in serum radioactivity and permits comparisons of different experiments.

TABLE I.—RADIOSODIUM AND WATER ANALYSES ESTIMATION OF EXTRACELLULAR PHASE—"SODIUM SPACE"—IN MUSCLE AND SKIN IN NORMAL AND SHOCKED MICE PREPARED WITH RADIOSODIUM 18 HOURS IN ADVANCE

	Muscle			Skin	
Extremity	Radio-activity (% dose/ gm. tissue)	Water content (gm./kgm.)	Apparent extra-cellular phase "sodium space" (gm./kgm.)	Radio-activity (% dose/ gm. tissue)	Water content (gm./kgm.)
			Normal		
(1)	(2)	(3)	(4)	(5)	(6)
Fore	0.602	740	—	1.495	585
Hind	0.507	733	—	1.37	556
A. (Serum	—)				
Fore	0.665	734	194	1.71	554
Hind	0.576	738	168	1.74	518
B. (Serum	3.3)				
Fore	0.671	741	155	1.92	554
Hind	0.667	733	153	1.67	561
C. (Serum	4.2)				
			Burn (of hind legs only)		
Fore	0.78	740	197	2.18	603
Hind	1.705	770	430	2.7	670
D. (Serum	3.8)				
Fore	0.846	762	—	2.13	591
Hind	2.276	798	—	3.54	764
E. (Serum	—)				
Fore	1.108	708	213	2.22	604
Hind	1.68	742	315	3.35	694
F. (Serum	5.1)				
			Tourniquet (to hind legs only)		
Fore	1.07	739	239	2.46	554
Hind	3.02	762	675	3.11	615
G. (Serum	4.3)				
Fore	0.765	736	167	1.98	579
Hind	2.55	791	556	2.78	684
K. (Serum	4.4)				
Fore	1.065	713	202	2.655	606
Hind	2.87	796	550	3.91	754
L. (Serum	5.0)				

TABLE II.—RADIOSODIUM AND WATER ANALYSES; ESTIMATIONS OF EXTRACELLULAR PHASE — "SODIUM SPACE" — IN MUSCLE AND SKIN IN NORMAL AND SHOCKED MICE 20 HOURS AFTER THERAPY WITH RADIOACTIVE 0.9 PER CENT SODIUM CHLORIDE

	Muscle			Skin	
Extremity	Radio-activity (% dose/ gm.tissue)	Water content (gm./kgm.)	Sodium space (extra-cellular phase) (gm./kgm.)	Radio-activity (% dose/ gm.tissue)	Water content (gm./kgm.)
			Normal		
(1)	(2)	(3)	(4)	(5)	(6)
Fore	1.9	710	224	1.75	610
Hind	0.915	746	172	2.015	620
M. (Serum	5.2)				
Fore	0.54	710	220	1.05	500
Hind	0.553	710	227	—	480
N. (Serum	2.4)				
Fore	—	—	—	—	—
Hind	0.81	700	199	1.78	505
O. (Serum	3.9)				
			Burn		
Hind	2.05	774	313	4.4	710
P. (Serum	6.3)				
Hind	2.8	785	318	6.9	724
Q. (Plasma	8.45)				
			Tourniquet (to hind legs only)		
Fore	2.7	710	210	5.16	535
Hind	11.3	810	880	9.66	770
R. (Serum	12.6)				
Fore	2.99	660	222	4.27	520
Hind	9.66	790	724	8.62	690
S. (Serum	13.1)				
Fore	2.11	730	128	3.68	532
Hind	10.06	820	612	8.00	720
T. (Serum	16.1)				

intracellular phase about 530 grams per kilogram; in injured tissues the apparent extracellular phase or "sodium space" increased to 700 grams per kilogram, leaving only about 130 grams per kilogram of nonsodium containing intracellular phase!

In the treatment experiment, furthermore, the values for radiosodium excretion by all routes showed a marked retention of sodium in the shocked mice in the 24 hours after therapy. Similar retention had also been noted in the patients with extensive burns treated with isotonic solutions of sodium salts (7). Accord-

TABLE III.—THE RETENTION OF RADIOSODIUM ADMINISTERED AFTER INJURY

Time of radioactivity count	Normal mice*	Burned mice*	Tourniquet mice*
Immediately after injection —hrs.	100	100	100
24	47	82	97
48	14	56	76
72	<1	24†	41
96		20†	30

Therapy consisted of a single intraperitoneal injection of a volume of 0.9 per cent sodium chloride containing radiosodium equal to 16 per cent of body weight. The dose was given from 1 to 2 hours after injury.

Counts of γ rays were made with the Geiger counter by placing the animal in a fixed position before a 3.5 mm. thick lead shield to exclude β rays. Each value is an average of 10 animals.

*The values are expressed in per cent of the amount of radioactivity in the animal immediately after injection.

†These values are unduly low because legs and tails containing radiosodium sloughed off from some of the mice. Three of these mice died.

ingly, this phenomenon was investigated further.

Shock was produced in groups of 10 mice by a standardized burn and by application and release of tourniquets on the hind legs (20). One hour later the injured mice which were in shock were treated with a dose of 0.9 per cent sodium chloride equal to 16 per cent of their body weight by a single intraperitoneal injection. A group of normal mice received a similar injection. The saline solution used contained radiosodium, and the total radioactivity of each animal was measured immediately after the injection and at 24 hour intervals thereafter. Thus excretion of the dose of sodium chloride is indicated by decreased radioactivity of the animal as compared to its initial radioactivity.[1]

The average values are shown in Table III and clearly demonstrate that in the first 24 hours the injured animals retained nearly all the sodium chloride injected. On the contrary the normal mice excreted over half the isotope and, since mixing of isotope and body sodium occurs fairly rapidly (15), presumably some of their original sodium was excreted in addition. The sodium retention persisted in the injured animals; 96 hours later these mice still contained more of the injected sodium than did the normal animals at 48 hours.

[1]The possibility of failure of absorption of the isotope from the peritoneal cavity of mice in shock is excluded by the data in Tables I and II showing that isotope administered after injury is absorbed and distributed throughout the tissues.

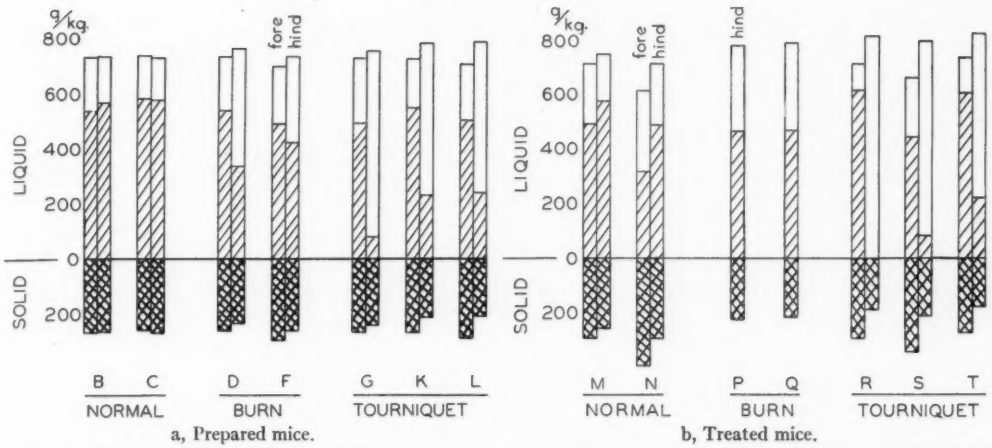
TABLE IV.—COMPARISON OF EXPERIMENTAL VALUES WITH CALCULATED VALUES FOR 1 KILOGRAM OF NORMAL MUSCLE INFILTRATED WITH VARIOUS INCREMENTS OF PLASMA (OR INTERSTITIAL FLUID)

	Water content (gm./kgm. tissue)	Sodium content (m.Eq./kgm.tissue)	Sodium space (gm./kgm. tissue)
Found in normal muscle	730	22	157
Calculated for 1 kgm. of normal muscle plus 250 c.c. of plasma	773	46	330
Found in muscle in burned mice	770	+56	+400
Calculated for 1 kgm. of normal muscle plus 500 c.c. of plasma	804	61	436
Found in traumatized muscle in tourniquet shock	796	+100	+700
Calculated for 1 kgm. normal muscle plus 1000 c.c. of plasma	820	81	570

DISCUSSION

The experiments in prepared animals trace the movement of sodium and water in essentially normal, untreated animals subjected to severe injury by burning or tourniquet trauma. The studies of Manery and Bale (15) and of Kaltrieder and associates indicate that equilibrium had been obtained between extracellular sodium and radiosodium in the 20 hours prior to injury, hence movement of the isotope represents movement of sodium. In the therapeutic experiments, 20 to 24 hours elapsed from the time of injection of radiosodium to analysis (and the animals were in good condition at that time), so that substantial equilibrium had been established. Some parallel gravimetric sodium analyses of tissues support this interpretation (8).

The data in Tables I and II clearly show the massive shift of sodium into injured tissues; it is apparent from the water analyses that relatively much less fluid was transferred. The computation of tissue "sodium space" shown in Figure 1, a and b, is based on the data of Hastings and associates (11, 14) which show that in tissues sodium is in a fluid in equilibrium with plasma, i.e., containing a similar concentration of sodium. The very high "sodium space" in tissues computed



a, Prepared mice. b, Treated mice.

Fig. 1. Redistribution of sodium in injured muscles. In each pair of columns the left represents muscles of both uninjured forelegs and the right muscles of both injured hind legs of mice in Tables I and II with serum analyses. Clear space indicates "extracellular phase"—assuming that sodium in normal and traumatized tissue is extracellular; diagonal lines, intracellular water; cross hatch, solids. (All measurements are expressed in grams per kilogram fresh muscle.)

In the injured tissues, the "extracellular phase" appears greatly increased with consequent diminution or disappearance of the intracellular compartment; apparently the antisodium barrier was demolished and extracellular sodium moved into the cells.

from the present data shows definitely that much of the sodium is in tissues *without* a proportionate increase in fluid. It appears that much of the tissue water has taken on this property of extracellular fluid; that is, that much of the sodium had become located within the cells. (Subsequent data (8) on potassium loss indicate an exchange of sodium for intracellular potassium.) Thus in traumatized tissues the conventional extracellular fluid space has been supplanted by a far larger "sodium space" composed of (a) extracellular edema fluid and (b) intracellular water containing excess sodium. In this way the sodium "loss" into a traumatized area far exceeds the fluid loss in relative and absolute values.[1]

This excess of sodium loss may be clearly discerned in Table IV, which shows the extracellular fluid volumes computed if 250 cubic centimeters, 500 cubic centimeters, or even 1000 cubic centimeters of plasma (or interstitial fluid) infiltrated into the extracellular compartment of 1000 grams of fresh muscle. The great influx of sodium after trauma may be appreciated when it is realized that a kilogram of muscle saturated with a liter of plasma would contain less sodium but more water than was found in our analyses of traumatized muscle.

The significance of the marked retention of therapeutically administered sodium becomes apparent when considered in relation to these tissue analyses. As a consequence of the sodium and fluid loss in the injured tissues, the extracellular compartments elsewhere in the body are depleted. The electrolyte and fluid redistribution is similar to that found by Darrow and Yannet in their experiments in which sodium was removed without loss of fluid. After injury, moreover, there is the added factor of extracellular fluid immobilized as edema in the injured area. Consequently, as much as half the total extracellular sodium in the body may have been removed from active circulation.[2] Accordingly, after administration of large amounts of isotonic solutions of sodium salts to the animal in shock, the deficit in available extracellular fluid is made up and only sodium in excess is

[1] We are indebted to Dr. Edith H. Quimby for the use of her portable counter (22) for bedside measurements of radiosodium in human burns. These indicated a great influx of sodium into burned tissues (8).

[2] It is noteworthy that although the amount of available extracellular sodium has been greatly reduced, no sodium has been removed from the body. Hence measurement of extracellular fluid volume with radiosodium shows no change inasmuch as a normal number of sodium atoms are still present to dilute the isotope when equilibrium is attained prior to therapy (8) when the plasma sodium concentration is substantially unchanged.

excreted. Thus little or no sodium is excreted in the urine by the severely injured animal (or patient), whereas most of the sodium given is promptly excreted by normals. When the amount of solution administered exceeds the volume of extracellular fluid depleted, the excess is excreted; this occurred when the injury was less extensive or the amount of solution exceeded 15 per cent of body weight, that is half the total extracellular volume.

Wiggers has stated that "reduction in the volume of blood returned to the heart is the keystone of all modern conceptions of shock." Extensive clinical studies (4) have shown that in human cases of shock, circulatory failure results from inadequate blood return to the heart because of the marked reduction in plasma volume. Decisive information as to the cause of this decrease in plasma volume is relatively meager, and the belief that plasma is "lost" into injured tissues is based on indirect evidence. For example, Beard and Blalock analyzed fluid obtained by centrifuging excised portions of injured tissues and found its protein content approximated and sometimes exceeded that of the plasma. On this basis they inferred that this fluid "escaped from blood vessels at the sites of injury," and in their paper "Reasons are given for believing that the loss of plasma proteins at the site of injury is the most important factor in the production of shock." Since tissues normally contain three times as much protein as plasma, the occurrence of proteins in tissue fluid does not necessarily prove their source is the plasma. More recent tissue analyses (8) fail to demonstrate an increase in proteins at the sites of injury and indicate instead that the proteins in the fluid from injured tissues came from the injured tissue cells themselves (1, 17). Another example of the inadequacy of the local plasma loss hypothesis is the report of Fine and Seligman that although a traumatized extremity of a dog gained 69 grams in weight, the plasma "loss" in the animal was 700 cubic centimeters—a tenfold discrepancy.

Gamble has emphasized the unity of electrolyte structure of extracellular fluid "composed of the plasma of the blood and the interstitial fluid (including lymph) which lies between the vascular compartment and the tissue cells." Furthermore there is clear-cut evidence (5, 8, 12, 16) that the volume of circulating plasma is in large part dependent upon the volume of extracellular fluid and its concentration of sodium. The mechanism which determines the relative size of the two fractions of extracellular fluid is not understood. Hopper, Elkinton and Winkler found that after equivalent reduction of extra-cellular fluid by (a) prolonged water deprivation and by (b) rapid salt depletion, there was a disproportionately greater reduction in plasma volume after (b) removal of sodium.

The present experiments demonstrate the very great accumulation and side tracking of sodium in injured tissues with subsequent reduction in plasma volume characteristic of traumatic shock. Conversely, treatment with an amount of isotonic sodium solution approximating one-half the extracellular volume restored this volume. On this basis, the successful treatment of shock in animals (20) and in man (7) with large volumes of isotonic solutions of sodium salts is explained.

SUMMARY

Radioactive sodium was used in mice to compare the sodium content of normal tissues and those injured by burning or by tourniquet trauma.

The sodium content of injured skin and muscle is greatly increased and exceeded the gain in water (edema). This indicated that additional sodium accumulated in the intracellular compartment.

As a result of the redistribution of sodium and water, approximately one-half the total amount of extracellular sodium was sidetracked and rendered unavailable. Administration of this amount of sodium by injection of 0.9 per cent sodium chloride containing radiosodium was followed by nearly complete retention of sodium in the injured animals but by excretion of sodium in normals.

The relationship between the reduction in plasma volume characteristic of shock and depletion of extracellular fluid is discussed.

The extensive and thorough biochemical studies of Tabor and Rosenthal have just appeared in *Public Health Reports*, April 6 and 13, 1945, 60: 378–381, 401–418. The close similarity of their data and ours is noteworthy.

It is encouraging to note that the latest recommendations (*Shock Report* No. 57) of the Subcommittee on Shock of the National Research Council for the treatment of extensive burns state: "Replacement therapy in the first 48 hours thus involves fluid volumes of these magnitudes, totally 8000 to 15,000 c.c. for the 48 hour period."

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AN ANALYSIS OF THE MASSACHUSETTS GENERAL HOSPITAL CASES OF LUNG ABSCESS FROM 1938 THROUGH 1942

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THE last report on lung abscess from the Massachusetts General Hospital showed evidence of improvement in the results of treatment during the 5 year period, 1933 through 1937, as compared with those of earlier reports (2). Sufficient time has now elapsed to include a 2 year period of follow-up after the next 5 year period, 1938 through 1942, and this report is offered for comparison with that of the preceding 5 year period.

Chart 1 gives a comparison of our experience with lung abscess arranged in periods, the first of 8 years (1), the second of 5 years (2), and the third of 5 years. Over the total period of 18 years covered by these three groups there has been a progressive rise in the number of patients cured and a corresponding drop in the number of patients who have died of the disease. There has been a less striking drop in the number of patients who remain alive with disease. These trends were particularly noticeable during the period 1933 through 1937 and were ascribed to certain factors such as improvement in the technique of the drainage operation, more prompt application of surgical treatment, and particularly the utilization of lobectomy when the case was thought to be unsuitable for drainage or when drainage alone had failed to effect a cure. It was pointed out also that all other types of operation such as thoracoplasty, redrainage after failure of the drainage procedure, and plastic procedures for closure of chronic cavities were unsuccessful. As a result of this experience these procedures were abandoned and during the next 5 year period reported upon here (1938 to 1942) the only surgical operations used were drainage and lobectomy, either primary or secondary.

In the present series 120 cases are reported. Chart 2 gives an analysis of the outcome of these 120 cases. Seventy-one (59.2 per cent) were cured. Of these there were 28 spontaneous or nonoperative cures (23.3 per cent of the entire group) and 43 cures resulting from operation (drainage, primary lobectomy, or lobectomy after drainage had failed to cure). Twenty-two patients died (18.3 per cent). Of these 11 died without operation and 11 died after operation. The remaining 27 patients (22.5 per cent) survived but were not cured. Six of these were not operated upon. Twenty-one were drained, but the operation did not result in cure and, for one reason or another, no subsequent lobectomy was carried out.

ANALYSIS OF THE 75 CASES OF PATIENTS WHO WERE OPERATED UPON

Seventy-five patients were subjected to operation, either primary lobectomy or drainage (Chart 3). In the latter group the only secondary operation resorted to in any case was lobectomy or pneumonectomy.

Primary Lobectomy Cases

In 15 cases (20 per cent) a primary lobectomy was performed. The reasons for choosing this operation were as follows: chronicity of the disease, 10 cases; hemorrhage, 2 cases; more than 1 lobe involved, 1 case; mistaken diagnosis of carcinoma, 1 case; abscess located in upper lobe, 1 case. The most frequent indication was the chronicity of the case. It was observed in the last report, as a result of a careful study of the duration of disease in each case, that no patient whose abscess had existed for 1 year or over recovered without surgery and that very few cases of such long standing responded to drainage alone. Of the 15 cases in the present series only 5 were of less than 1 year's duration. Three had been going 1 to 2 years; 3 had existed 2 to 5 years, and 2 were known to have existed longer than 5 years. In 2 cases the duration was not known.

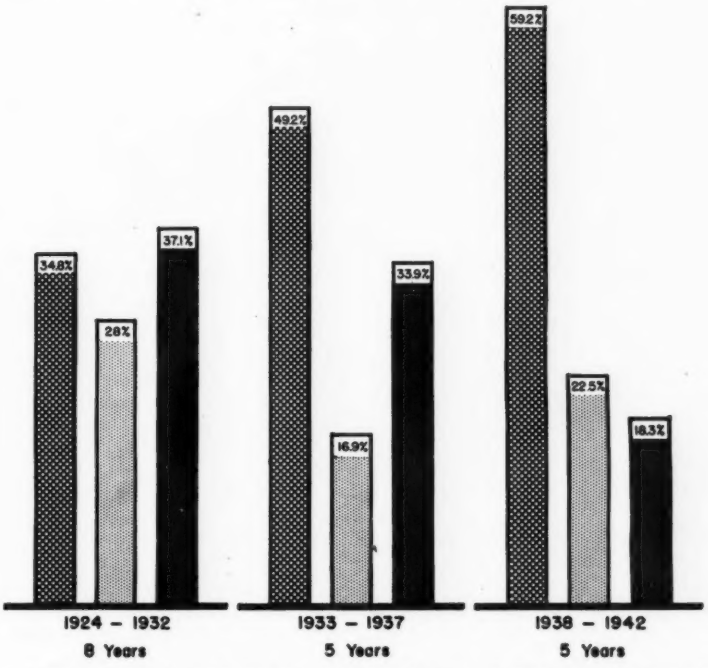

Chart 1. Comparison of experience with lung abscess at the Massachusetts General Hospital during 3 periods of observation. Dark dots indicate cured; light dots, alive with disease and black areas, deaths.

Serious hemorrhage led to the choice of lobectomy in 2 cases because experience has shown that massive hemorrhage is one of the important causes of death in cases of lung abscess. It may occur after drainage as well as before and packing cannot be relied upon to stop it.

The location (right upper lobe) or extent of the disease led to the choice of lobectomy in two cases and in one case the preliminary diagnosis was carcinoma. In this case, however, the lesion was found on exploration to be a lung abscess and a lobectomy was performed.

Technique. One of the characteristics of lung abscess is that it is associated with an immense hyperplasia of the hilar lymph nodes and marked inflammatory induration of all adjacent structures including the tissues surrounding the pulmonary vessels. Because of this it was impossible to carry out a dissection and separate ligature of these vessels in 10 of the 15 cases and the tourniquet method of dealing with the structures at the hilum had to be used.

Postoperative course. Of the 10 patients in whom the tourniquet technique was used, 2 died of sepsis (spreading pneumonitis in one and subphrenic abscess and peritonitis in the other). Of the 8 survivals in this group an empyema developed in 6. In only 3 of these was adequate chemotherapy used. In the remaining 2 patients primary healing resulted. These both had chemotherapy.

In the 5 patients who had individual ligation and separate bronchial closure using silk technique throughout, there were 4 uncomplicated recoveries and 1 case of empyema. The latter case was the only one of the five in which sulfa drugs were not used.

In all the cases of empyema following both types of technique, recovery was complete though delayed. All patients in this group remain cured.

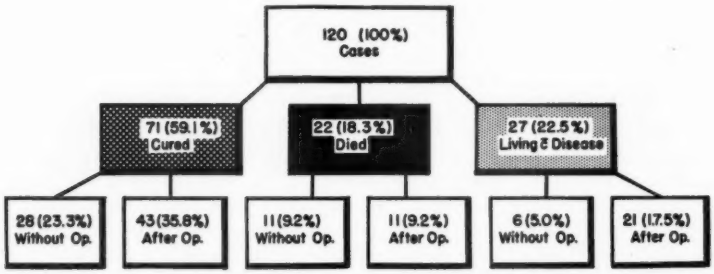

Chart 2. Total experience with 120 cases of lung abscess, including all methods of treatment.

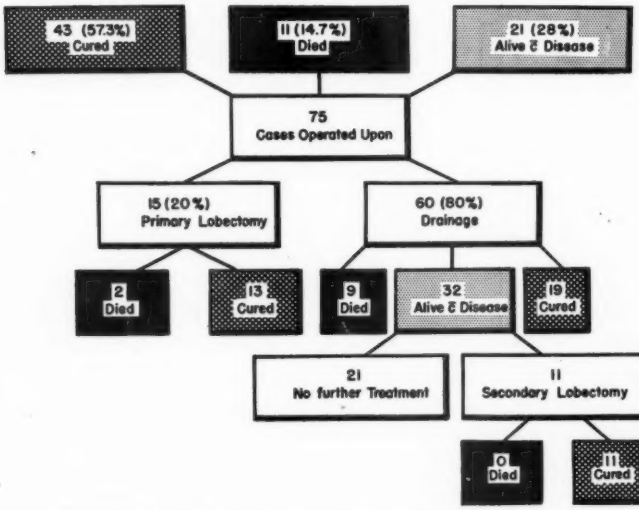

Chart 3. Results of surgical treatment in 75 cases of lung abscess.

In the last previously reported series of 125 cases (1933 to 1937), primary lobectomy was employed in 6 patients, 1 of whom died. The ratio of postoperative deaths is approximately the same in the present group and, if both are added together, making 21 cases of primary lobectomy with 3 deaths in all, we find a postoperative mortality of approximately 1 of 7 patients operated upon.

Drainage Cases

In the remaining 60 cases drainage of the abscess was performed. The method described in the last report (2) was followed without modification. In 15 cases a one stage procedure was used, while in 45 cases the two stage operation was performed.

The results of drainage in these 60 cases, like those of the last reported series, were disappointing in spite of the fact that the great majority of the patients were operated upon soon after they were admitted to the hospital. Chart 4 shows that of the entire group of 75 patients treated surgically 40 were operated upon within the first 2 weeks and 63, within the first month after entry. As a result of drainage 19 patients were cured, 9 died, and 32 are classified as alive with disease. The last group includes those with a persistent cavity or bronchocutaneous fistula. Eleven of these

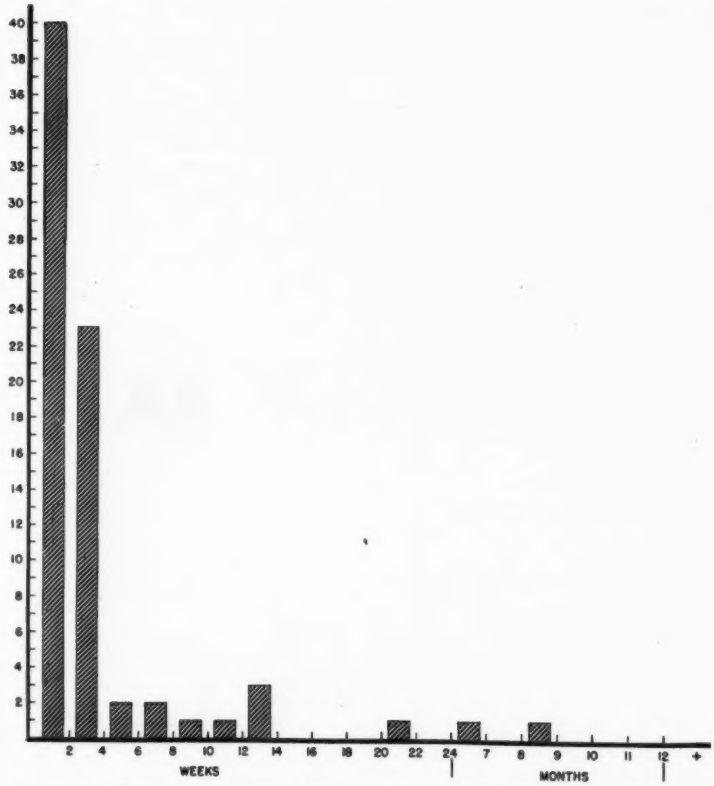

Chart 4. Elapse of time between date of entry to hospital and date of operation.

patients were cured subsequently by secondary lobectomy or pneumonectomy. There were no deaths following this procedure.

As before, the criteria of cure were freedom from cough and expectoration, disappearance of abnormal physical signs, and x-ray evidence of complete healing.

Causes of death after drainage operation. As is characteristic of any series of lung abscess cases, the most frequent cause of death after the drainage of the abscess was spreading infection in the lung. This occurred in 5 cases. Massive hemorrhage was responsible for 2 deaths and brain abscess for one death. The only postoperative fatality which can properly be ascribed to the surgical procedure was the one patient who died suddenly while on the operating table. In spite of a definite rule of the thoracic service that all patients with lung abscess must be operated upon with the head lower than the feet, the operation in this case was carried out in the sitting position. On incision of the lung there was a sudden collapse resulting in coma followed promptly by death which was attributed to cerebral air embolism. This fatality must therefore be ascribed to technical error.

The *postoperative mortality* of the drainage operation in this series, inasmuch as all but 1 patient died of the progression of his disease, is therefore 1 in 60 cases, or 1.7 per cent.

Lobectomy After Failure of Drainage to Cure

In the majority of patients who had persistent disease following drainage, a lobectomy was advised. The operation was carried out in 11 of these. Analysis of the reasons for not operating upon the 21 others reveals that 8

Chart 5. Spontaneous cure cases: elapse of time from onset of disease to date of entry to hospital.

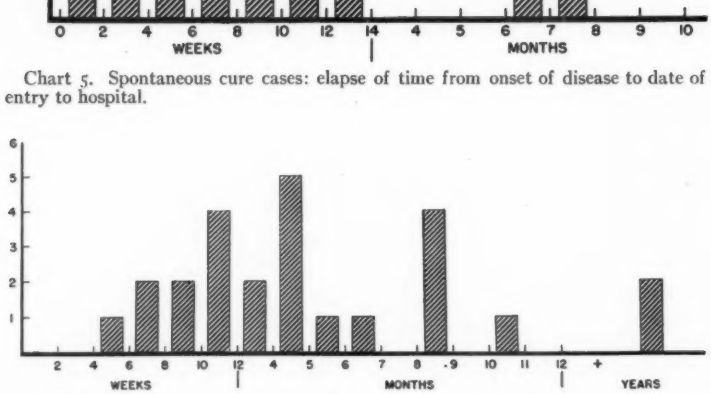

Chart 6. Spontaneous cure cases: elapse of time from date of onset to date of proved cure.

patients were working full time and were unwilling to give up their jobs. Four patients stated that they had so few symptoms that they were satisfied to remain as they were. In 1 case an attempt was made to perform a lobectomy, but the operation was abandoned because of technical difficulties arising from widespread vascular adhesions. The proportion of secondary lobectomy operations carried out would no doubt be greater during a period of more unemployment than existed from 1937 to 1942.

Of the 11 patients operated upon none died. All were cured. In 2 cases there was primary healing. In these the operation was carried out by the vessel ligation, bronchus suture technique, silk being used. In all the others there was a complicating empyema which ultimately healed. The tourniquet method was used in all of these but 2, and in these 2 cases chromic catgut mattress sutures were used. This method of bronchial closure has since been given up and supplanted by the use of fine silk sutures over the end of the bronchial stump (method to be reported).

ANALYSIS OF THE 45 CASES OF PATIENTS WHO WERE NOT OPERATED UPON

Of the 45 patients who were not operated upon 28 recovered spontaneously, 11 died, and 6 remained alive with disease because they refused operation. The causes of death in the group of 11 patients who died were overwhelming infection in 6, brain abscess in 4, and complicating ulcerative colitis in 1. Operation was not advised in this group because of the fact that these patients were all hopelessly ill. Two died in less than 24 hours after arrival.

Twenty-eight patients recovered without surgery (23.3 per cent of the entire group). That there was not an unusually large percentage of very early cases is shown in Chart 5 which illustrates the duration of the disease from its onset to the date of entry of the patient to the hospital. It is interesting, however, that in the majority of these cases the disease was of 3½ months' duration or less. A more important fact is demonstrated by Chart 6 which shows that the total duration of the disease in many of the spontaneous cure group was of surprising length. Although 9 patients recovered in 3 months or less, there were 8 in whom the disease lasted 3 to 6 months and in 6 patients from 6 to 12 months. Two patients recovered after the expiration of 1 year.

The usual symptomatic treatment, bed rest, and postural drainage were employed in this group. In only 5 was adequate sulfa drug chemotherapy used.

SUMMARY OF ANALYSES

This group of lung abscess cases represents the latest of a series of reports from the Massachusetts General Hospital dealing with this disease. It brings to 681 the total number of cases reported from this hospital.

Table I gives a comparison of the results in each of the last 3 groups. Certain interesting observations can be made from it. First, there has been a definite increase in the total number of cures by all methods of treatment. The present figure is 59.2 per cent as compared with 49.2 per cent for the last series and 34.8 for the one before that. There was a corresponding fall in the number of deaths, the present figure being 18.3 per cent as compared with 33.9 per cent in the last series reported. This represents a much more pronounced drop in mortality than occurred between the last two reports. The percentage of spontaneous cures remains approximately the same, 23.3 per cent.

There was a further drop in the operative mortality after the drainage procedure to 1.6 per cent. This is in line with the experience of other clinics. The percentage of cures resulting from surgery continues to increase, reaching a figure of 35.8 per cent of the entire group of 120 cases. On the other hand, there was no significant change in the percentage of patients operated upon. There was a relative increase, however, in the number of patients on whom a primary lobectomy was performed. Of this group there were 15 cases as compared with 6 in the last series and none at any time before that.

TABLE I.—COMPARISON OF RESULTS OF PRESENT GROUP WITH PREVIOUSLY REPORTED SERIES

	1924–1932 Per cent	1933–1937 Per cent	1938–1942 Per cent
Cured	34.8	49.2	59.2
Died	37.1	33.9	18.3
Alive with disease	28.0	16.9	22.5
Cured spontaneously	21.4	19.3	23.3
Cured by surgery	12.8	29.9	35.8
Operative mortality (drainage cases)	12.5	7.4	1.6
Number of patients operated upon	45.7	68.5	64.8

TABLE II.—USE OF SULFA DRUG CHEMOTHERAPY

	No. of cases	No. receiving sulfa drugs	Percentage
Entire series	120	43	35.8
Those cured	71	21	29.5
Those who died	22	6	27.3

Influence of sulfa drug medication. Sulfa drug chemotherapy began to be used during the period covered by this last series. The possible influence of the use of these drugs in increasing the percentage of cures and decreasing the percentage of deaths must be considered. The administration of one of these chemotherapeutic agents in adequate dosage was carried out in 43 or 35.8 per cent of the entire group of 120 cases. The total number of patients who recovered as a result of all forms of treatment was 71. Of this group 21 received sulfa drug therapy. Therefore, 29.5 per cent of those who recovered received these drugs. Of the entire series 22 died and 6 of these patients were treated with sulfa drugs, making 27.3 per cent. It is obvious that there is no significant difference in these figures. One is forced to conclude, therefore, that the use of sulfa drug chemotherapy made no material change in the results in this series. Table II summarizes these data.

CONCLUSIONS

Although lung abscess continues to be a serious disease, there has occurred over the

past 10 or more years an encouraging increase in the number of cures and a gratifying reduction in the mortality rate. That this improvement in the results of treatment is probably not due to the influence of the administration of sulfa drug chemotherapeutic agents is strongly suggested by the data presented. The improved results, if not due to a diminution in the virulence of the infection in the average case, are most likely accounted for by a greater knowledge of the disease and a better understanding of the principles of treatment. The fact that the management of these cases in the Massachusetts General Hospital has for many years been the responsibility of a very small group may be of significance.

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POSTOPERATIVE PROPHYLAXIS OF RECURRENT MAMMARY CANCER WITH TESTOSTERONE PROPIONATE

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THE effect of hormones upon the production, growth, and treatment of cancer has been studied by innumerable laboratory and clinical workers. Recently, these investigations have culminated in the important results obtained in patients with cancer of the prostate by castration and the subsequent use of synthetic estrogenic hormones.

ENDOCRINE DYSPLASIAS OF THE BREAST

In women the breast is undoubtedly one of the most hormone-sensitive organs. Certain changes of the breast, whether transient or chronic in character, have been described under different names and are considered today by various investigators as functional or endocrine mastopathy. On this basis, the following mastopathies can be grouped together: Cheatle and Cutler's mazoplasia, Reclus' cystic disease, Schimmelbusch's cystic adenoma, Aschoff's "mastopathia chronica fibrosa cystica," and numerous other syndromes.

Semb pointed to the high incidence of cancer in cases of fibrous cystic mastitis which he called "fibro-adenomatosis cystica mammae." Many workers before him, however, had suggested that inflammatory breast disease might have a tendency toward becoming malignant.

On the basis of the work of Cotte, Pallot, and Berard (which in turn is based on earlier research of Leriche and of Wanke and Paulsen, of Dahl-Iversen, and of many others), estrogens began to be used in the years 1935 to 1937 not only in cases of simple painful breasts, but also in cases of Reclus and Schimmelbusch disease. There were some favorable reports on this therapy, but results varied greatly and even were disastrous in some cases. I saw 1 successful case and 10 failures.

Further research disclosed the reason for these varying results. Functional mastopathy results from a disturbance of the hormonal balance which may have various causes. Benzadon recently classified mastopathies according to the etiology involved, as follows: (1) excessive blood estrogen, (2) excessive luteal hormone in the blood, (3) ovarian insufficiency, (4) of thyroid origin, (5) of pituitary origin, (6) of other origin. He estimates that about 50 per cent of cases of mastopathy are caused by hyperestrinism. In my opinion, this percentage is even larger because it would seem that the amount of estrogenic hormone fixed by the mammary glands should be taken into consideration as well as the estrogen level of the blood. The presence of a larger amount of estrogen in the mammary glands depends on the ability of this organ to store the hormone in a way which is not strictly related to the amount in circulation. It is obvious that in the case of hyperestrinemia, the mammae are likely to contain an excessive amount of hormone. Be this as it may, the failure of the treatment of mastopathy with estrogen is understandable.

The fibrous cystic mastitis which occurs in rats after estrogen treatment casts new light on this question. Incidentally, the same condition has been observed in both men and women. This confirmed the important rôle estrogen plays in the production of mastopathy. I had the opportunity of seeing two women with mastopathy undoubtedly caused by excessive estrogen therapy. In 1937, I made the same observation in the case of a man, 49 years of age, suffering from a stomach ulcer, who had received estrogen treatment for 6 months. This treatment resulted in mammary hypertrophy necessitating surgical intervention; histologic examination showed fibrous cystic mastitis in both glands. The influence of the estrogenic hormone on mastopathy can often be proved by estrogen in the particularly large cysts seen in this disorder.

The use of the antagonistic hormone, testosterone, gives extraordinary results in most

From the Escola Paulista de Medicina.

cases of mastopathy. This therapy was only started in 1937 following the papers of Desmarest and Capitain (22, 23) which are based on findings in 17 cases.

In 1938, I started to use testosterone propionate in the treatment of mastopathy and observed that 80 per cent of the patients reacted favorably, not only as far as the pains in the breasts were concerned, but also with regard to the hardening of the glands. There were no large cysts or papillomatous proliferations (patients with such conditions were operated upon). In the remaining 20 per cent, no improvement occurred. After having treated 45 patients in this way I am convinced that the estrogenic hormone is not always responsible for the disorder. Since I have adopted the classification of Benzadon, the results have improved.

MASTOPATHY AND CANCER

Many clinicians have described the development of cancer in cases of mastopathy. However, they do not agree on the percentage in which this occurs. Semb reported a 24 per cent incidence of cancer in cases of cystic papillomatous mastopathy. Cheatle and Cutler estimate that 20 per cent of the cases of mammary cancer have their origin in mastopathy, whereas Ewing reports 50 per cent.

Besides Semb's monograph, 2 other fundamental investigations have been published on this subject, one by Lindgren, the other by Korpássy.

Lindgren calls attention to the confusion existing regarding the nomenclature. In agreement with the majority of other authors stating that most women are subject to mastopathy, he finds such mammary changes very common, as shown by his statistics on 60 autopsies of women between the ages of 35 and 75 years. However, he encountered only 8 cases of pronounced epithelial proliferation.

Korpássy found at autopsy pathological changes in the mammary glands in two-thirds of a group of 300 women between 14 and 89 years of age. He found epithelial hyperplasia in 154 mammary glands, typical papillomas in 10, and cancer in 2.

Semb has stated that cancer develops particularly in cases of cystic papillomatous mastopathy, but this does not exclude its occasional occurrence in other forms of mastopathy.

Recently (1944), Cole and Rossiter classified the various types of mastopathy (chronic mastitis) and added: "since we have observed carcinoma develop in areas of precancerous hyperplasia, and have encountered this type of lesion in 15 or 20 per cent of our cases of carcinoma of the breast, we are convinced that there is a definite relationship between carcinoma and chronic cystic mastitis, particularly in the type which we have described as 'precancerous hyperplasia'."

My opinion (38, 39) is similar to that of these writers. On the basis of studies of 15 cases of mastopathy in which I performed "plastic amputation,"[1] 12 biopsies, and 76 cases of cancer which were accompanied by mastopathy (86 per cent), I believe that Cole and Rossiter's classification adequately sets forth the present opinion with regard to the relationship between mastopathy and cancer. In 4 out of the 15 patients with mastopathy who underwent operation, cancer was present. A particularly interesting case among these was that of a woman, 26 years of age, who had a tumor of several months' duration located in the uppermost part of the left breast. Palpation verified the presence of a hardened zone which showed only a slight degree of opacity on transillumination. Special attention was given because even though a diagnosis of chronic mastitis had been made, there were two pea-sized nodes in the corresponding axilla. A biopsy was made, with extirpation of the mammary tissue and removal of one of the lymph nodes. Histologic examination revealed chronic cystic mastitis with increased epithelial hyperplasia. Examination of the axillary nodes revealed metastases of solid carcinoma. Radical operation was performed, and when the removed tissue was carefully examined a single nucleus of solid carcinoma smaller than a bean was revealed.

In my opinion the existence of mastopathy of the papillomatous type, or the detection of a papilloma, as revealed by transillumination, suffice to warrant suspicion of a malignant tumor, whether the breast is bleeding or not.

[1]This operation consists of the amputation of the mammary gland followed by transplantation of adipose tissue of the abdomen and free graft of the nipple so that an esthetic reconstruction (39) is accomplished.

The other forms of mastopathy cannot actually be considered as precancerous, although they do not exclude the possibility of cancer.

Accepting Cole and Rossiter's statement as a fact, that 20 to 30 per cent of cases of mastopathy are of the "precancerous hyperplasia" type, the real relationship between cancer and mastopathy can be estimated. Recently, Warren studied 1,044 cases and states that cancer occurs 4.5 times more often in individuals with mastopathy than in healthy women. In his recent book, Geschickter devotes a long chapter to the relationship between chronic cystic mastitis and cancer and cites the following points in support of the tenet of the existence of a causal relationship between mammary dysplasia and cancer:

"1. In many cases breasts removed for cancer show the changes of some form of chronic cystic mastitis either grossly or microscopically.

"2. Transitional stages between the two conditions have been traced by histologic investigation.

"3. In the experimental production of mammary cancer in mice, using estrogenic hormones, mammary changes resembling those found in cystic disease and adenosis precede the cancerous changes.

"4. Among patients treated conservatively for mammary dysplasia, a number develop mammary cancer subsequently."

Studying my cases with these points in mind I became convinced of the evident relationship between the two afflictions.

1. In 88 cases of mammary cancer, a microscopic examination of the histologic specimens revealed mastopathy in 76 cases, or 86 per cent.

2. In 6 cases of mastopathy with pronounced epithelial hyperplasia, the diagnosis was very difficult because there were borderline tumors, and cancer was diagnosed in 4 cases, one of which was confirmed by the existence of axillary metastases.

3. There is no fundamental argument against the assumption that the spontaneous development of cancer in human beings goes through the same process as does experimental cancer in rats.

4. In 1 case of simple mastopathy which was verified histologically, cancer developed after 4 years.

My personal conviction, therefore, is that a causal relationship between cancer and certain cases of mastopathy exists, and that estrogen is a causative factor in the development of cancer. If this is so, it is logical that the occurrence of cancer is higher in cases of mastopathy because hyperestrinism exists in almost every instance in both diseases.

EXPERIMENTAL CANCER PRODUCED WITH ESTROGENS

In 1932 Lacassagne (31) produced experimental cancer of the mammae in rats by injecting estrogens. The changes in the mammary tissue are progressive, with cyst formation and eventually epithelial proliferation which results in cancer. Lacassagne demonstrated the importance of the constitutional predisposition, since in the strains most susceptible to cancer, the initial changes started in the second month, formation of cysts occurred in the third, and cancer developed in the fifth month; while in the less susceptible strains there were no changes before the third month, and cancer occurred only in the fifteenth month.

Numerous investigators have confirmed this observation. Burrows produced mammary cancer in 2 male rats by applying estrone to the skin. Lewis and Geschickter, according to Benzadon, found that an extract of cancerous mammae of women contains considerable amounts of estrogen (6 rat units per gram).

The use of estrogens as a carcinogenic agent has become routine, and some laboratories use such material for the production of experimental mammary cancer. Cook and associates list estrone with the carcinogenic substances. Moreover, the entire chemical group of phenanthrene compounds is considered carcinogenic, and it is known that this grouping forms part of the chemical nucleus of the ovarian hormones.

In 1938, Lacassagne (32) published statistics covering his investigations carried on since 1932 on tumors produced experimentally with estrogens. He concluded that mammary cancer is produced by estrogens only in strains with a tendency to spontaneous cancer; however, in such strains, the normal incidence of cancer is increased and the disease seems to develop earlier than usual in both male and female animals.

Geschickter, in reporting his experimental investigations, states that "the percentage of rats in which estrogenic mammary cancers develop varies, but when the animals survive the required time, the disease may be present in 100 per cent of the survivors under certain

experimental conditions." He used rats from a colony of more than 5,000 animals (maintained on a standard diet and inbred for a period of 7 years) in which spontaneous mammary cancer did not occur. He also found that the total dose required to produce mammary cancer is not influenced by the size of the daily dose but varies with the duration of estrogen action of different estrogen compounds and with the method of administration.

ESTROGENS AND HUMAN CANCER

After Lacassagne's experiments, the question immediately arose as to whether or not estrogens used therapeutically could cause cancer. There are a very few cases on record in which this is with more or less certainty reported to have occurred after estrogen had been used, especially in cases of mastopathy (1936 to 1937). It is difficult to arrive at definite conclusions in this respect. On the basis of the doses (total 10 to 20 mgm.) used experimentally in rats for the production of cancer, tremendous doses would seemingly be required to produce a similar effect in human beings.

Recently, we observed a case of mammary cancer in a woman, 35 years of age, who had been treated with estrogen continuously for 5 years (progynon, 10,000 I.U., three times a month). The possibility of a cancerogenic influence of the estrogenic hormone cannot be eliminated in this case. In some other cases of mammary cancer observed, the women had been treated with estrogens too, but the doses used were too small to warrant ascribing any cancerogenic effect to the estrogens.

ANTAGONISM BETWEEN ESTROGENS AND TESTOSTERONE

In 1926, Steinach, Kun, and Peczenik presented some evidence of an antagonism between estrogens and testosterone. Later, Moore and Price postulated that this antagonism might result from an inhibitory action of the androgen upon the pituitary with a resultant diminution or cessation of the ovarian production of estrogen. This interpretation does not eliminate the possibility of an actual biologic antagonism, and the fact that the action may be indirect does not detract from its possible therapeutic significance.

Lacassagne (33) used testosterone in animals in an attempt to prevent the production of cancer caused by simultaneously administered estrogen. In the beginning, when using testosterone acetate in small doses, he did not succeed. He resumed his experiments with testosterone propionate in a dose 7 to 8 times that of the estrogen, giving doses of 2 milligrams per week continuously until the death of the animal. Out of 18 females which survived for a period of 1½ to 18 months, not one developed cancer. Several other investigators have since confirmed this antagonism between the two hormones. Peralta Ramos in 1939 demonstrated the antagonism between testosterone and estrogen in rabbits, and arrived at the conclusion that 1 milligram of testosterone propionate is capable of neutralizing approximately 50 rat units of estrogen. Geschickter was unable to prevent the occurrence of mammary cancer in his experiments, probably because he used insufficient doses of testosterone. Recently Benzadon confirmed the antagonism clinically and experimentally.

TESTOSTERONE IN INOPERABLE AND RECURRENT CANCER

Testosterone has been used only recently in the treatment of human cancer and little literature on this subject has been published. Ulrich, in 1939, reported 2 cases of mammary cancer in which he used testosterone acetate. In the first case, besides a cancer of the left breast which had been diagnosed clinically and confirmed histologically, appreciable changes were found in the right breast, apparently indicative of cystic mastitis of a high degree. Moreover, the pathologic examination of the removed left breast revealed that the cancer had developed on the lesions of chronic mastitis. This patient, who had complained of severe pains in the right breast as well as in the right arm, which had gradually become emaciated, improved in a sensational manner after the operation following 10 injections of 10 milligrams of testosterone acetate. Ulrich's second case is also most interesting. This was a case of cancer of the right breast infiltrating the whole organ and with axillary involvement (clinical diagnosis). In the other breast two well circumscribed tumors were found. Since

the patient also had a uterine myoma, accompanied by hemorrhage, hysterectomy and bilateral castration was performed. The mammary cancer was considered inoperable at the time. Upon treatment with 10 injections of testosterone acetate, all the subjective symptoms disappeared, and the right breast improved so much that it was considered operable.

In spite of the criticism that can be made with regard to these 2 cases, the fact remains that they are the first that called attention to this subject. Another paper was published by Loeser, also in 1939, in which he reported recovery after the administration of 1500 milligrams of testosterone in 2 patients with supraclavicular recurrence of cancer after a previous operation for mammary cancer. In 1942, Farrow and Woodard reported the treatment of 33 patients with mammary cancer and bone metastases, who responded to relatively small doses of testosterone—5 to 10 milligrams once or twice a week, to a total of 10 to 12 injections. These writers report relief of the pains.

In 1944 Fels made a new contribution, by using large doses of testosterone propionate within a short period of time in 3 cases of cancer, 2 of which were recurrences and 1 of which was inoperable. In the first 2 patients relief of pain and other symptoms were obtained, and in the third (ulcerated tumor), deodorization and reduction of pus.

In my own experience, inoperable cases require a perfect "follow up." In general I prescribe testosterone propionate for those patients who are being attended at home but who are not under my strict personal supervision. I can confirm that the pain diminishes to such an extent under this therapy that narcotics become unnecessary.

PROPHYLAXIS OF RECURRENCES

Because of the results obtained in many cases of mastopathy with testosterone and because I was convinced of the relationship between this disease and mammary cancer, I planned, in April, 1939, to use testosterone as a postoperative measure in mammary cancer for the prevention of recurrences. I started using testosterone[1] in several patients with unilateral mammary cancer and mastopathy of the other breast.

To date, we have treated 63 patients with mammary cancer who had previously been operated upon. Treatment was started in 49 patients more than 1 year ago, in 12 more than 4 years, in 4 more than 5 years, and in 24 more than 3 years ago. It is believed that in view of this experience, an appraisal of the results obtained to date is warranted.

As controls, 64 cases are reported in which the breast had been removed by the same technique of radical surgery during the period of 1932 to 1939, and in which testosterone propionate was not used.

All 127 cases were operable and corresponded to Stages I and II of the clinical classification[2] which I adopted.

All but one case (No. 42229) underwent generous mastectomy with extensive removal of skin and aponeurosis, resection of the pectoralis major and minor, and dissection of the cellulolymphatic tissue of the axilla from within outward, removing all these parts in a single piece. The adipose-cellular tissue under the clavicle and as far as the supraclavicular region, which is inaccessible to dissection, was always coagulated electrically. In some cases a flap of the abdominal skin was used since it was impossible to make a perfect suture by simply stitching the wound.

PATHOLOGIC ANATOMY AND HISTOLOGIC GRADING OF MALIGNANCY

In all 127 cases histopathologic examinations were made.

To date, no agreement regarding the classification of tumors has been reached. Great confusion exists often preventing a complete understanding between pathologists of different countries and even of different clinics. Since the classification of mammary carcinoma is no exception, the system which I have adopted should be described.

In my opinion, the ideal classification from a practical point of view is one which is not

[1]Testosterone propionate was used throughout, usually as neo-hombreol. Other preparations were used only in some cases.

[2]An anatomoclinical classification based on both clinical examination, including transillumination, fluoroscopy, etc., and pathological examination. The cases are divided into 6 stages: (1) tumor localized in the mamma; (2) movable axillary metastases; (3) obstructing axillary metastases; (4) movable supraclavicular metastases; (5) obstructing supraclavicular metastases; (6) distant metastases or excessive extension of the localized lesion. This classification is of value as a basis for statistics since it leaves no doubt as to the presence or absence of axillary metastases, the degree of infiltration being confirmed histologically.

Fig. 1.

Fig. 2.

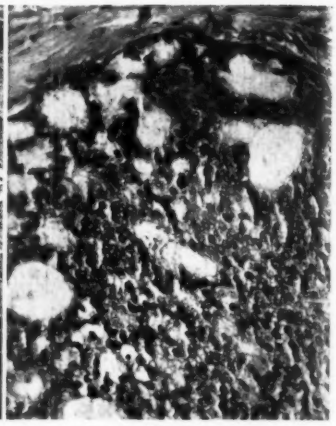

Fig. 3.

Fig. 1. Papillary cystoadenocarcinoma. Objective, 3; ocular, 4; bellows, 40.

Fig. 2. Papillary cystoadenocarcinoma. Note the adenomatous proliferation of the stroma which seems to be a simple exaggeration of the picture of chronic cystic mastitis. Objective, 8; ocular, 6; bellows, 30.

Fig. 3. Papillary cystoadenocarcinoma. Note an island of proliferation demonstrating the fact that cells do not show any signs of anaplasia. Objective, 40; ocular, 6; bellows, 30.

confused by details of secondary importance but is focused on the essential morphologic characteristics of the tumor indicating the degree of maturity or, better, of differentiation. This leads automatically to a grading of malignancy because lack of differentiation approaches anaplasia.

With due appreciation of the work of Broders (6–15) who established a numerical grading of malignancy, I believe that the method of this investigator is complicated and not clearly enough expressed. It seems to me that a "malignogram" made along the lines of a "hemogram" is not advisable. As a matter of fact, each blastoma represents a specific degree of malignancy, but it is not inappropriate for purposes of diagnosis and statistics to classify tumors in groups according to their malignancy, which method has been accepted since Hanseman.

In accordance with Borst's system (3–5) I accept for all practical purposes the classification of Amorim based on the degree of differentiation and anaplasia of tumors. This classification would establish four degrees or types for each tumor, the use of which would facilitate the grading of the malignancy in agreement with Broders' original division into four degrees.

We have the following classification for carcinoma of glands including those of the breast:

1. Adenoma malignum: Grade I of histologic malignancy
2. Carcinoma adenomatosum: Grade II of histologic malignancy
3. Carcinoma solidum: Grade III of histologic malignancy
4. Carcinoma diffusum or meristoma: Grade IV of histologic malignancy

The "adenoma malignum" (Figs. 1–3) constitutes the most differentiated form of glandular cancer and is so called because of the similarity to simple adenoma. Its malignancy is characterized by a heterotopic and destructive growth. It can produce metastases in certain organs (uterus, rectum). In the breast the prognosis is comparable to that of a benign tumor and some authors consider it sufficient simply to extirpate the gland. I have never seen metastases in such cases. The diagnosis of adenoma malignum is difficult because the heterotopy is not as easily distinguishable as in the hollow organs (uterus, rectum, etc.). Borst (4) and Heiberg claim that there are certain cytologic characteristics which make a differentiation between these tumors and benign adenomas possible: in-

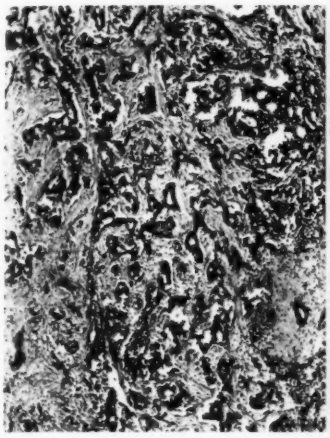

Fig. 4.

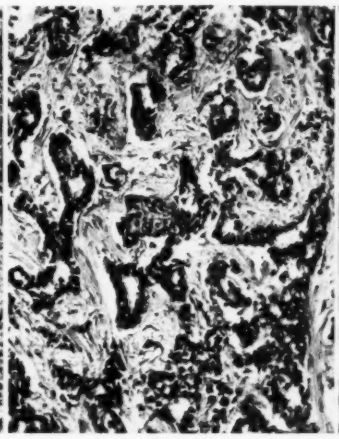

Fig. 5.

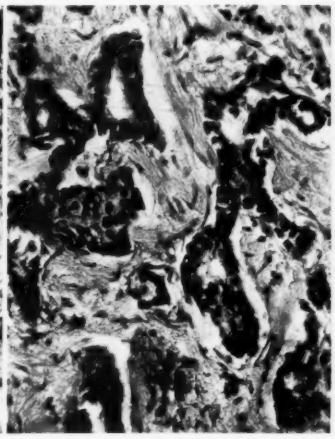

Fig. 6.

Fig. 4. Scirrhous carcinoma. The neoplastic foci form little blocks reproducing the tubular formations when observed with a central light. Objective, 8; ocular, 4; bellows, 52.

Fig. 5. Scirrhous carcinoma. The glandular appearance is more plainly seen in this photograph. Objective, 20; ocular, 4; bellows, 52.

Fig. 6. Scirrhous carcinoma. A certain degree of cellular anaplasia may be seen. Objective, 40; ocular, 4; bellows, 45.

crease in the dimensions of the nucleus and changes in its form and arrangement.

The "carcinoma adenomatosum" (Figs. 4–6) is a glandular malignant tumor in which, however, it is possible to identify the "mater" tissue. Although proliferation of the epithelium occurs in an irregular and disorderly fashion, the tumor has an inner luminosity (alveolar arrangement). The cellular "restlessness" is evident. There is a notable increase in the cellular dimensions, with marked polymorphism. One can find monstrous nu-

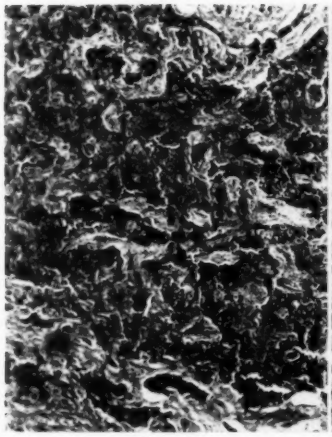

Fig. 7.

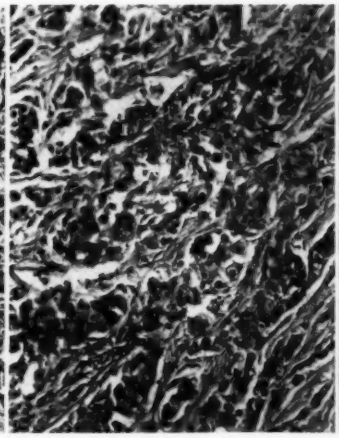

Fig. 8.

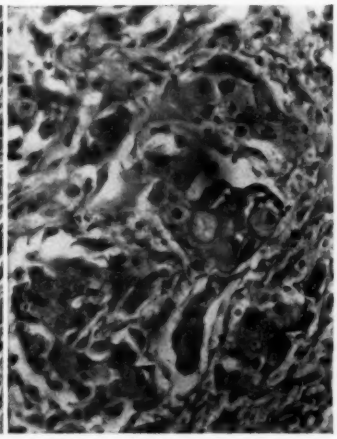

Fig. 9.

Fig. 7. Note the invasion of the connective tissue by solid blocks and cells. Objective, 8; ocular, 6; bellows, 35.

Fig. 8. The cellular anaplasia is prominent. Objective, 20; ocular, 6; bellows, 35.

Fig. 9. The irregularity of the form and size of the cells, particularly of the nuclei, shows that there is a high degree of anaplasia present. Objective, 40; ocular, 6; bellows, 30.

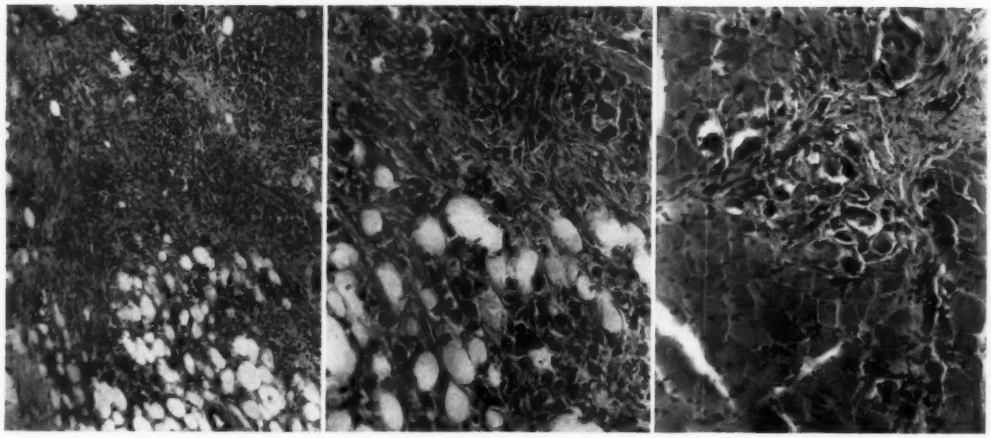

Fig. 10. Fig. 11. Fig. 12.

Fig. 10. Infiltration of the connective and fat tissue by isolated cells. Objective, 8; ocular, 6; bellows, 35.

Fig. 11. Note in this section light degree of cellular anaplasia. Objective, 20; ocular, 6; bellows, 35.

Fig. 12. Infiltration of the musculus pectoralis major by the neoplastic cells. Objective, 20; ocular, 6; bellows, 35.

clei emitting numerous "mitoses." The tumors produce metastases after a relatively long localized stage.

The "carcinoma solidum" (Figs. 7–9) constitutes a more common morphologic type of mammary cancer. It represents a higher degree of nondifferentiation than the tumor just discussed. The proliferous cells, however, do not lose the characteristics of the epithelium, but form solid blocks or cords, and there is no inner luminosity reminiscent of the glandular structure from which they originate. Sometimes this makes it difficult to distinguish these from certain epidermoid tumors. The atypical cytologic appearance is even more distinct, and granulated structure, vacuoles, etc. can be found in the cells.

In the "carcinoma diffusum" (Figs. 10–12) called "meristoma" by Fischer-Wasels the epithelial characteristics disappear completely, the contiguity of the cells forming rows or budding masses. The cells spread into the connective tissue, sometimes retaining the cubic or cylindric shape, but frequently keeping their round or globular appearance. The differential diagnosis from sarcoma is not always easy, for which reason Fischer-Wasels tried to combine these tumors with the carcinomas and sarcomas into one group, the "meristomas."

The above classification is made according to a system. The pure forms are rarely found. Sometimes one tumor can have the appearance of two consecutive grades. Zones of adenoma malignum and areas of carcinoma adenomatosum are often found together but on no occasion have carcinoma diffusum and adenoma malignum or carcinoma adenomatosum been found to coexist.

It is logical that when two forms coexist, the grading of malignancy should be made according to which kind predominates. If both forms occur to the same degree, this should be indicated by an intermediate grade. In a case of mammary tumor, for instance, in which carcinoma adenomatosum and carcinoma solidum occur to the same extent, the grading would be II–III.

This method of grading is, of course, open to criticism. One of its weak points is that the reaction of the connective tissue is not taken into consideration. I agree that a scirrhous carcinoma differs from a medullary tumor. The development of the clinical case will differ in the same way as the sensitivity to radiation.

I believe, however, that these considerations should be thought of as secondary, since there is not the slightest doubt that the degree of differentiation of the epithelial elements reflects much more clearly the degree of malig-

nancy of a carcinoma than does the connective tissue reaction. The reaction of the stroma should, however, always be stated in the histologic reports because it constitutes to a certain degree an indication of defense against malignant proliferation.

Recently I have checked this system of grading clinically in a study of 308 cases of mammary cancer which were reported to the "Associação Paulista de Medicina." The postoperative results observed over a period of more than 5 years were for each stage of malignancy as follows: grade I, adenoma malignum, 100 per cent; grade II, carcinoma adenomatosum, 60 per cent; grade III, carcinoma solidum, 23.4 per cent; and grade IV, carcinoma diffusum, 0 per cent.

SUMMARY OF RESULTS

As mentioned, 63 patients with mammary cancer (grades I and II) were treated with testosterone propionate after having undergone radical mastectomy. Of these, 49 patients had been operated upon more than 1 year ago. Space limitations prohibit their detailed report. However, the accompanying tables and case reports summarize the over-all results obtained.

COMPLETE REPORT OF SIX CASES

CASE No. 40,039. I.T., 43 years of age, married, came for first consultation on December 26, 1939. Clinical diagnosis: carcinoma of a left supernumerary breast. Upon physical examination the clinical stage could not be determined exactly because of the extreme obesity of the patient. The patient had always had a small spot below the left breast but paid no attention to it until she noticed it growing and forming a tumor about 3 months before. Examination revealed a hardened, aberrant left breast, the size of a hen's egg, with an irregular surface. No change in the normal breast could be observed by palpation or x-rays. Lymph nodes in the corresponding axilla appeared not to be involved. The clinical examination was not conclusive because of the patient's extreme obesity. Menstruation occurred every 28 to 30 days and lasted 3 to 5 days. There had been two normal deliveries and one miscarriage.

At first operation on January 30, 1940, the supernumerary breast with its tumor was extirpated. Pathologic examination revealed a diffuse macrocellular carcinoma (meristoma), with abundant cells. The tumor showed atypical nuclei, numerous mitoses, and intensive proliferation of the connective interstitial tissue. There were numerous intrusions into the lymphatic and blood vessels. The connective periglandular tissue showed tumorous infiltrations radiating into all directions. Even the fat tissues were infiltrated by neoplastic elements, grade IV of histologic malignancy (Prof. Moacyr Amorim).

A few days after the surgical intervention a diffuse infiltration of the subcutaneous tissue near the external borderline of the left breast was noted, and various lymph nodes the size of an olive were found. Because of the high degree of malignancy of the neoplasm shown by this immediate postoperative development, radical mastectomy was decided upon.

At the second operation on February 29, 1940, the breast was amputated—the Halsted operation being used with transverse incision of the axilla.

Pathologic examination confirmed the diagnosis made from the earlier examination, great infiltrations of the cellular tissue and metastases in various lymph nodes were found. Treatment with 50 milligrams of testosterone propionate per week was started during hospitalization in March, 1940. In May, 1940, an axillary tumor near the latissimus dorsi was noticed. Roentgen-ray therapy was started, and the treatment with testosterone propionate was stopped upon the patient's request. In July, lymph nodes in the supraclavicular fossa became palpable, and hepatic metastasis developed shortly thereafter. The patient died September 16, 1940, with symptoms of cerebral metastasis. The total dose of testosterone propionate that she had received was 350 milligrams.

CASE No. 40,117. I.F., 34 years of age, married, came for first consultation on April 5, 1940. The clinical diagnosis was carcinoma of the right breast, clinical stage II. The patient had never experienced any symptoms in the breast until 2 months before, when she noticed a hardened zone in the right breast. She treated it with hot compresses and cream without obtaining any improvement. Examination revealed a tumor of the whole right breast which was hard and turgid, and increased in size, but palpation revealed no fluctuation nor were there pains either spontaneous or upon pressure. At the level of the axilla numerous lymph nodes were felt. Menstruation was very scanty, lasting 1 to 2 days, and irregular, often with a delay of 5 to 10 days. There had been one normal pregnancy.

Operation, performed on May 11, 1940, consisted of an extensive amputation of the breast with axillary dissection and transplantation of abdominal skin in order to close the thoracic wound. Partial rupture of the sutures occurred a few days after operation. Pathologic examination revealed the neoplasm to be carcinoma diffusum with axillary lymph node involvement, grade IV of histologic malignancy. On May 30, 1940, patient was released from the hospital. Ambulatory treatment was given until July 7, 1940, at which time the wounds had healed completely. During this period 20 milligrams of testosterone propionate per week was administered. The further course of the patient was uneventful until March, 1942, although the administration of

Fig. 13. Case 42229. Parallel sections of breast. In one of the distal parts a voluminous tumor mass the size of a baby's fist was found. A typical fibrous capsule surrounds the tumor, separating it completely from the adjacent tissues.

testosterone propionate was irregular because of long periods of amenorrhea. On April 5, 1942, the patient was brought to the hospital as an emergency case. Roentgenographic examination revealed pathologic fracture of the fifth dorsal vertebra. Complete immobilization was impossible because of the patient's extreme obesity. Roentgen-ray castration was performed and also irradiation of the vertebral column which, however, brought about only slight relief of pains. In October, 1942, the patient developed pneumonia and died on October 27, 1942. The total dose of testosterone propionate administered was 500 milligrams.

Case No. 41,221. L.C., 41 years of age, married, came for first consultation on July 19, 1941. The clinical diagnosis was cancer of the left breast, clinical stage II. The patient had developed a tumor in the left breast approximately 1½ months ago. She had felt no pain, but the progressive growth of the tumor worried her. Upon examination a tumor the size of a nut was found at the external borderline of the left breast. Transillumination showed a dark spot without any apparent demarcations. Various enlarged lymph nodes were found in the axilla, some of which seemed to be an axillary extension of the mammary gland. Menstruation occurred every 26 to 28 days and lasted 2 or 3 days. There had been three normal deliveries.

Operation on July 23, 1941, consisted of radical mastectomy. The postoperative course was normal. Pathologic examination revealed a carcinoma diffusum with axillary lymph node involvement, grade IV of histologic malignancy. Treatment with testosterone propionate, 50 milligrams per week, was started immediately. The patient was released from the hospital August 2, 1941. In April, 1942, pains in the vertebral column started. Roentgenograms showed no changes at all and the patient underwent treat ment for rheumatism. In June of the same year, the rachialgia became worse, and the patient also complained of cough. Roentgenographic examination revealed metastases at the level of the 11th dorsal vertebra and in the lungs. At that time the patient was suffering from amenorrhea and admitted to have interrupted the testosterone propionate treatment, since she attributed her illness to that drug. She was advised nevertheless to take 175 milligrams per week. Unfortunately, she followed the advice of another physician who considered this treatment inadvisable. The patient's condition deteriorated in spite of the use of radiotherapy; dyspnea developed and the general state of health rapidly became worse. The patient died in cachexia at the end of October, 1942. Total dose of testosterone propionate was presumably 1,200 milligrams.

Case No. 42,092. N.R., 43 years of age, married, came for first consultation on March 10, 1942. Clinical diagnosis: cancer of the left breast; clinical stage II. For 3 months she had noticed a tumor of the left breast. She consulted a doctor who made a biopsy from which he made the diagnosis of "cancer." Upon examination a large tumor without any definite demarcations was found. It was located at the outer borderline of the breast and the skin adhered to it; an infiltration of the cellular fatty tissues along the borderline of the breast was observed. The lymph nodes of the axilla were found to be enlarged, the largest being the size of a nut, although it was freely movable. The patient suffered from menorrhagia, lasting 6 to 8 days, with intervals of 25 to 28 days. There had been 6 normal pregnancies.

At operation March 12, 1942 radical mastectomy was carried out. She was released from the hospital on March 24, 1942, on which day treatment with testosterone propionate, 75 milligrams per week, was started. Pathologic findings: carcinoma diffusum with lymph node involvement, grade IV of histologic malignancy. Patient returned on August 7, 1942, complaining of severe pains in the vertebral column and edema of the left arm. Roentgenographic examination revealed metastases at the level of the 7th dorsal vertebra. Upon palpation of the supraclavicular fossa, a hard tumor was found which was scarcely movable and seemed to be fixed to the lymph nodes of that area. In the axilla and near the latissimus dorsi spreading to the back, an infiltration of the cellular subcutaneous tissue was observed. Roentgen-ray castration was performed and roentgen-ray therapy was used for the various affected areas, but it was not possible to establish a satisfactory dose since the patient's general health was deteriorating. In October, 1942, the patient began coughing and expectorated blood. At this time a new tumor was found at the level of the 5th intercostal space below the zone of operation, and dissemination of small tumorous nodes had occurred not only into the axillary region and anterior wall of the chest, but also into other distant regions of the tegument. Patient died on January 9, 1943. The total dose of testosterone propionate could not be determined accurately but it did not exceed 1,000 milligrams.

Fig. 14.

Fig. 15.

Fig. 16.

Fig. 14. Same case. Comedocarcinoma of ducts, with diffuse infiltration. Low power. Marked interstitial sclerosis between cancerous cystic formations. Small sclerotic capsule formation around the smaller focus. Inside this capsule a strong lymphocytic infiltration is visible. A small focus shows small adenocancerous proliferation with solid cords progressing toward the tissue of the capsule.

Fig. 15. Same case, same slide, slightly higher power. This field shows small areas of cancerous proliferation, around which a kind of a capsule of fibrous tissue has formed in which lumps of parvicellular elements sometimes develop (mainly lymphocytic).

Fig. 16. Same case, same slide slightly higher power. Cancerous focus or larger adenocancer, also surrounded by the same type of "capsule," vaguely outlined and showing in the central part a necrotic appearing substance with areas of visible calcification, showing black on the picture. Acini of the normal mammary gland and thickened areas or sections of sclerosis between the adenocancerous foci are visible.

Case No. 42,229. M.S.S., 41 years of age, married, (Fig. 13 to 28) came for first consultation on September 5, 1939. Clinical diagnosis: carcinoma of the right breast; clinical stage II. At the end of 1938, a biopsy of the right breast was made in another hospital, and on the basis of this a diagnosis of

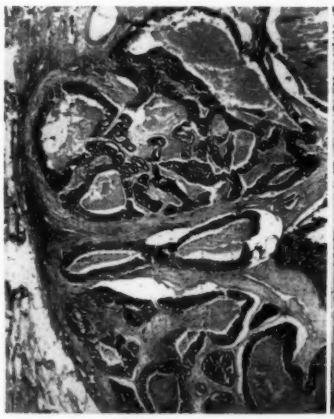

Fig. 17.

Fig. 18.

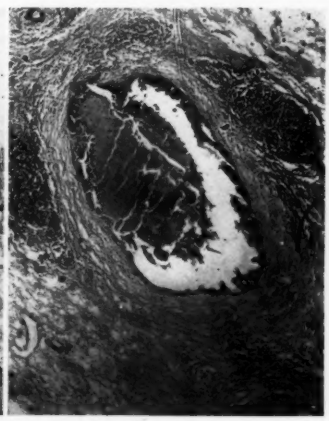

Fig. 19.

Fig. 17. Same case, same slide slightly higher power. This field shows numerous adenocancerous formations with a voluminous necrotic center separated by thickened fibrous sections. Note, however, in the periphery, corresponding to the skin of the nipple region, the formation of a genuine fibrous capsule separating the cancerous focus almost entirely from the subcutaneous tissue.

Fig. 18. Same case, same field as in Figure 15, slightly higher power. Two very small foci or cancerous nests. One of these particularly, is surrounded by a fibrous capsule and lymphocytic accumulations which form lymphocytic nodes.

Fig. 19. Same case, same slide, moderate magnification. This field shows identical picture as in Figure 20.

Fig. 20.

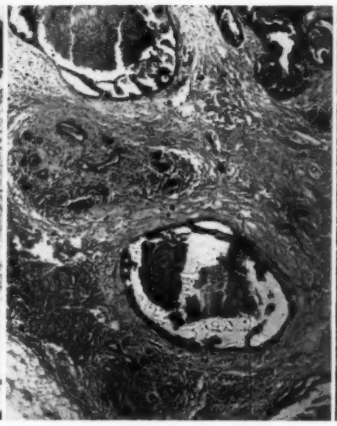

Fig. 21.

Fig. 22.

Fig. 20. Same case, same slide, moderate magnification. This field shows small areas of cancerization next to the acini, which still appear normal.

Fig. 21. Same case, same slide, field adjacent to that of Figure 20, showing the same phenomena. Some small characteristically adenocancerous foci are located next to a small lobe with acini which still appear normal. The other acini or tubular formations are difficult to classify (possibly cancerous?).

Fig. 22. Same case. Different field showing various cancerous proliferations—some cancerous nodes grow as if enveloped by the fibrous tissue (part of a large one is shown at the lower right corner and a smaller one in the lower left quadrant). In the upper left corner there is a small focus in the center of the connective tissue capsule which is infiltrated by a small, solid cancerous cord.

"glandular epithelioma" was made. The patient did not consent to operation and was treated with injections, the content of which was unknown to her. She specified during her first visit to this hospital that she would not be subjected to surgical intervention. Examination revealed a hard tumor of the right breast about the size of a baby's fist without any definite demarcation, fixed to the skin, particularly at the level of a nearby scar. Two pea-sized lymph nodes were found in the axilla. The entire

Fig. 23.

Fig. 24.

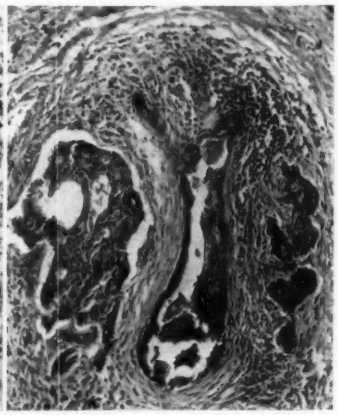

Fig. 25.

Fig. 23. Same case, same field as Figure 18, higher power. Cancerous cells in the small central focus and surrounding fibrous capsule.

Fig. 24. Same case, same field as Figure 20, higher power. The acini at top are almost normal. At bottom, as if connected with above structures, are tubular formations with proliferations or epithelial buds of cancerous appearance.

Fig. 25. Same case, same field as in Figure 14, higher power. In the center is a small tubular formation, apparently isolated by connective tissue. There are cancerous proliferations around it, which grow and form solid lumps, infiltrating the surrounding connective tissue.

Fig. 26.

Fig. 27.

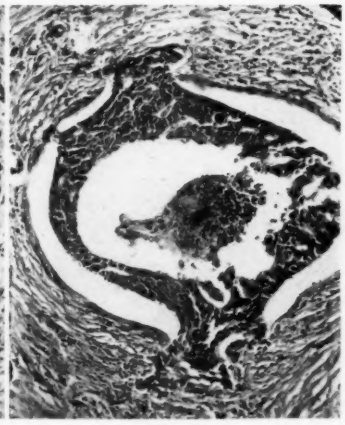

Fig. 28.

Fig. 26. Same case, same slide as that of Figure 14 but different field and higher power. Cancerous proliferation surrounded by a connective tissue capsule.

Fig. 27. Same case. Atypical epithelial proliferations, apparently cancerous, growing in tubular formation. They seem to be pseudopapillar but do not infiltrate the surrounding capsule.

Fig. 28. Same case. This figure shows the fight of the fibrous tissue against the epithelial penetration. There are two points, one at top and one at bottom, where the fibrous ring is incomplete and seems to be attempting to isolate the neoplastic focus more completely.

area of the tumor appeared dark upon transillumination, without definite lines of demarcation. Menstruation was of the 28 to 32 day type and lasted 3 to 4 days. No pregnancies.

Testosterone propionate, 175 milligrams per week, was administered. In October, 1939, the patient had a menstruation of 1 day's duration followed by 2 days during which the flow was of a clear, slightly pink color. Thereafter, she suffered from amenorrhea. Nevertheless, the same dose of testosterone propionate was continued until March, 1940, at which time she had received approximately 5,000 milligrams. Another examination revealed a definite local improvement—the tumor became circumscribed and detached from the skin; the axillary lymph nodes could no longer be palpated. In spite of the extremely high dose of androgenic hormone, no signs of virilization developed. At that time the dose was reduced to 75 milligrams per week which was continued through 1940, during which year the patient had only one menstruation lasting only 1 day.

In February, 1941, signs of virilization developed: hypertrichosis of the legs, thighs, and abdomen and enlargement of the clitoris. No voice changes were noted, but the patient was not questioned, in order not to cause new apprehensions. The dosage of testosterone propionate was then further reduced to 30 milligrams per week and this was continued until May, 1942. At that time the patient was in a good condition of health and the local conditions kept improving. However, the size of the mammary tumor did not decrease. The patient, who was worried about the symptoms of virilization and amenorrhea, finally agreed to surgical intervention on condition of not being completely disfigured. Having heard about "plastic amputation" she insisted upon such an operation. In spite of the serious objections which could be raised against such a procedure, I decided to perform this operation in view of the favorable clinical development and the patient's attitude.

At operation on June 7, 1942, a simple amputation of the mammary gland was performed and only the aponeurosis of the pectoralis major was extirpated. Thereupon a transplantation of the adipose tissue taken from the abdomen as well as a free graft of the nipple properly prepared was made. The area was immobilized by a special plaster arrangement. On June 27, 1942, upon removal of the plaster, a perfect integration of both grafts was observed. The patient was released from the hospital on July 1, 1942.

The following is the pathologist's report on the extirpated material:

1. Specimen consists of mammary gland, part of skin and aponeurosis. When cut vertically along parallel lines, a voluminous tumor mass about the size of a hen's egg is seen in a distal location. This area is of nodular character, the adjacent tissues being macroscopically clearly circumscribed as if surrounded by a capsule of skin and fatty tissue and separated widely from the aponeurosis. Most nodes have a grayish appearance, some are brownish red. The consistency is hard and firm in some sections and very soft in others.

2. Cuts parallel to the former disclose one or more smaller nodes the size of a grain of corn, proximal to the main tumor node. One of these smaller nodes had a cystic appearance and was filled with a liquid of chocolate color and of gelatinous consistency.

3. In the other sections the mammary gland below the nipple area and in the opposite half is extremely sclerotic, hard in consistency and whitish of color, yet there are no nodes of tumorous appearance.

The histologic examination revealed the following: Sections taken from various regions of the mammary gland all show the same picture characterized by extensive areas of sclerosis and hyalinization of the gland with a high degree of edema and softening of the tissue in some sections. In the center of these areas there are some isolated acini or glandular lobes, atrophic and lost in the density of the sclerotic zones. In the sections some ducts, also surrounded by connective tissue, are particularly conspicuous, which, however, are very dilated, sometimes cystic and lined with very proliferated epithelium. The latter consists of small and irregular cells which sometimes resemble the basic cellular elements. When sectioned on a tangent, the epithelium appears very thick almost obliterating the light and thus revealing the restless appearance of such cells. There is, however, no rupture of the basal layer.

Sections taken from the tumor masses show large epithelial structures, generally cystic in appearance, formed by glandular proliferated epithelium of atypical character and filled with pinkish contents of a necrotic or hyalinized appearance. These masses are surrounded by epithelial strings or lines which infiltrate the adjacent connective tissue in various directions. Some of these assume an adenomatous appearance. At other points, there are lines of islets of epithelial, atypical or anaplastic cells in the dense connective tissue. The stroma resembles large arrows of connective hyalinized tissue which forms fibrous rings around the epithelial growths. There are small nodes of calcification in the stroma. Nearby, close to the fatty tissue, it can be noticed that the neoplasia is in progress under formation of dilated ducts with the atypical appearance mentioned but always wrapped in strings of fibrous tissue forming a kind of fibrous capsule around them.

Diagnosis: carcinoma of the ducts of the mammary gland. High degree of atrophy and sclerosis of the mammary gland. Observations: characteristics of a not very pronounced anaplasia, grade II of histologic malignancy (Prof. Moacyr Amorim).

After surgical intervention, treatment with testosterone propionate was started in September, 1943, after the patient had menstruated 3 times. The dosage administered at that time was 30 milligrams per week. On June 29, 1944, the patient was doing well, had had no recurrences, but had had amenorrhea since April. The appearance of the reconstructed breast was satisfactory. The total dose of testosterone propionate was 7,800 milligrams.

CASE No. 43,044. W.A.L., 46 years of age, married, came for first consultation on January 25, 1943. Clinical diagnosis: cancer of the right breast; clinical stage II. Patient had noticed for some time at the level of the right breast the appearance of a small tumor to which she attached no importance. Its rapid growth, however, caused her to come to this clinic. Examination showed a large increase of the size of the mammary gland, which was rigid, and the mobility of the skin over the deep tissue had disappeared. Palpation revealed that the whole mammary gland was transformed into a hard tumor which seemed to be fixed to the deep layers. On transillumination a very dark spot, which occupied the entire area, could be seen. In the axilla, numerous lymph nodes, some the size of a pigeon's egg, could be palpated. Menstruation was of the 28 day type lasting 5 days. There had been five normal pregnancies.

At operation on January 28, 1943, a radical amputation of the breast was performed, followed by plastic surgery, an abdominal flap being used to make up for the excessive loss of substance of the tegument. The postoperative period was normal. The patient was released from the hospital on February 8, 1943. On February 1, 1943, treatment with 175 milligrams of testosterone propionate per week was started.

Pathologic findings: Carcinoma diffusum with lymph node involvement, grade IV of histologic malignancy. In April, 1943, patient began having amenorrhea, wherefore the dosage of the hormone was reduced to 75 milligrams per week. On May 8, 1944, the patient was doing well and showed no recurrence on clinical examination. On August 20, 1944, the patient was brought to the hospital after having complained for several days of intense pains at the height of the lumbar column. On that occasion, the presence of metastases in the column was observed radiologically and lymph nodes in the supraclavicular fossa on the side operated upon were palpated. The dosage of testosterone propionate was again increased to 175 milligrams per week. The patient is being followed up continuously.

OBSERVATIONS

The results obtained when testosterone propionate was administered after mastectomy are much better than when this postoperative treatment was omitted. One may call it a 100 per cent improvement. This figure is not absolute, since the number of observed cases is still rather limited and other factors may have interfered. There is, for example, the possibility of a fortunate series of operations or that of a technical superiority of the surgery which may have to be considered. Improvement in surgical technique in this series cannot be eliminated entirely as a contributing factor. However, if this were the case, one would have to assume that the technique, acquired over many years of practice, has been superior during this particular and limited period of time as compared with that used in the earlier cases not treated with testosterone propionate.

TABLE I.—GENERAL STATISTICS

Forty-nine patients operated on (Clinical Stages I and II) and treated postoperatively with testosterone propionate for more than 1 year.

Years since operation	Number of patients operated on	Number of patients followed up	Recurrences	Survival without recurrences	
				No.	Per cent
1–2	10	10	1	9	90
2–3	15	13	2	11	84.6
3–4	12	11	—	11	100
4–5	8	6	2	4	66.6
More than 5	4	4	—	4	100
Total	49	44	5	39	88.6

Comparison of our results after testosterone propionate treatment with the data from the best clinics not using this postoperative therapy shows the superiority of our method.

In my opinion, there exists sufficient clinical and experimental evidence to justify the conclusion that testosterone propionate has a prophylactic effect against recurrences of mammary cancer after operations.

The mechanism of this effect has not yet been explained definitely. However, in view of the atrophy of the anterior pituitary in rats after testosterone administration as observed by Lacassagne (33) and others, and the hypothesis of Moore and Price, that the pituitary plays an intermediary rôle, it seems probable that the effect of testosterone in mammary cancer is mediated through the pituitary gland.

For the interpretation of the inhibitive or prophylactic effect of testosterone propionate against recurrences of mammary cancer, it is necessary to consider two types of cases: (1) that in which all neoplastic elements are removed; and (2) that in which there are remaining neoplastic elements.

TABLE II.—RESULTS WITH AND WITHOUT TESTOSTERONE PROPIONATE

Patients with clinical stages I and II during a postoperative period of more than 3 years.

Testosterone propionate treatment	Period	Number of patients	Number of patients followed up	Recurrences	Survival without recurrences	
					No.	Per cent
Yes	1939–1941	24	21	2	19	90.4
No	1932–1939	64	45	24	21	46

TABLE III.—RESULTS WITH AND WITHOUT TESTOSTERONE PROPIONATE

Patients with and without axillary metastases during a postoperative period of more than 3 years.

Testosterone propionate treatment	Axillary metastases	Number of patients	Number of patients followed up	Recurrences	Survival without recurrences	
					No.	Per cent
Yes	No	5	5	—	5	100
Yes	Yes	19	16	2	14	87.5
No	No	9	7	—	7	100
No	Yes	55	38	24	14	36.8

If the operation performed is entirely radical, i.e. all neoplastic elements are removed, a recurrence can occur only by extension of malignancy to the opposite breast, where the tissue "mater" still exists. This would mean that the recurrence of the tumor is not brought about by remnant neoplastic cells, but rather, by the formation of a new tumor on the basis of pre-existing cancerogenic factors. According to observations, estrogens seem to be the principal cancerogenic element with respect to the mammary gland. Therefore, the biologic neutralization of the estrogenic element by testosterone would partly remove the danger of recurrence.

In cases in which neoplastic elements remain after operation, one of the phenomena observed after the administration of testosterone propionate is the formation of dense fibrous tissue, as mentioned by Fels and observed by me in case No. 42229, in which fibrous capsules were actually found. It is probable that this process limits or even prevents the development of further neoplastic tissue by destruction of the tumor through

TABLE IV.—RESULTS WITH AND WITHOUT TESTOSTERONE PROPIONATE

Patients with clinical stages I and II during a postoperative period of more than 4 years.

Testosterone propionate treatment	Period	Number of patients	Number of patients followed up	Recurrences	Survival without recurrences	
					No.	Per cent
Yes	1939–1940	12	10	2	8	80
No	1932–1939	64	45	25	20	44.4

TABLE V.—RESULTS WITH AND WITHOUT TESTOSTERONE PROPIONATE

Patients with and without axillary metastases during a postoperative period of more than 4 years.

Testosterone propionate treatment	Axillary metastases	Number of patients	Number of patients followed up	Recurrences	Survival without recurrences	
					No.	Per cent
Yes	No	2	2	—	2	100
Yes	Yes	10	8	2	6	75
No	No	9	7	1	6	85.7
No	Yes	55	38	24	14	36.8

complete blocking. This interpretation is merely a hypothesis which must be confirmed by further observations before it can be accepted definitely.

The process of fibrosis directs attention to the difference between the reaction of the scirrhous and of the medullar tumor to testosterone propionate. Clinically, no difference was observed, but histologically it appears that the organism makes an effort to block the tumor by proliferation of fibrous tissue, in which case testosterone propionate can only enhance this process. As to tumors rich in cells (medullar), fibrosis would constitute a beneficial factor, probably for the purpose of defense, as has been mentioned.

TABLE VI.—RESULTS WITH AND WITHOUT TESTOSTERONE PROPIONATE DURING A POSTOPERATIVE PERIOD OF MORE THAN 3 YEARS[1]

Patients classified according to their grade of histologic malignancy.

Testosterone propionate treatment	Histologic malignancy	Number of patients	Number of patients followed up	Recurrences	Survival without recurrences	
					No.	Per cent
Yes	I	2	2	—	2	100
Yes	II	6	6	—	6	100
Yes	III	13	10	—	10	100
Yes	IV	3	3	2	1	33.3
No	I	5	4	—	4	100
No	II	11	7	2	5	71.4
No	III	42	26	18	8	30.7
No	IV	6	4	4	—	——

[1]The results observed in patients during a 5 year postoperative period are not listed since there are only 4; all survived without recurrences.

TABLE VII.—DOSAGE OF TESTOSTERONE PROPIONATE GIVEN AS PROPHYLAXIS AGAINST RECURRENCES AFTER MASTECTOMY

Axillary metastases	Grade of malignancy	1st year	2nd year	3rd year	4th year	5th year
		mg	mg	mg	mg	mg
absent	Grade I	25	—	—	—	—
absent	Grade II	50	25	25	25	25
absent	Grade III	75	50	50	25	25
absent	Grade IV*	100	75	75	50	50
present	Grade I*	50	25	25	25	25
present	Grade II	75	50	50	25	25
present	Grade III	100	75	75	50	25
present	Grade IV	175	100	75	75	50

*These types have never been observed.
Note: Maintenance of the dosage used during the fifth year indefinitely after that time is recommended.

It appears that the observations made in our 63 cases warrant the establishment of some rules for the prophylactic use of testosterone propionate after mastectomy. Large doses have to be used over a long period of time. While first reluctant to use large doses, particularly in young women, because of fear of virilization, we are now inclined to believe that such side effects are of secondary importance in cancer and that they occur only in a comparatively small percentage of patients and with little intensity. Virilization was observed in 9 of 49 patients mastectomized more than 1 year ago; last year only 1 such patient was observed in a group of 14. It must be pointed out, however, that we do not draw the patient's attention to such phenomena, in order to avoid nervous upsets which might be detrimental to the continuation of the treatment.

Of a total of 10 patients showing signs of virilization, the phenomenon was severe in 5, moderate in 3, and questionable in 2. In the cases considered as severe, hypertrophy of the clitoris and hypertrichosis occurred; in the moderate cases, hypertrichosis only occurred. As to the questionable cases, they were classified as such because the patients insisted that they had observed an increase in hair growth. No change in the timbre of the voice was ever observed. The attention might be called to the fact that virilization occurred essentially in young women only; 9 were under 40 years of

age and only 1 was more than 40 years old (case No. 42229). Virilization occurred when the weekly dose was above 30 milligrams and the total dose reached 800 to 1500 milligrams of testosterone propionate.

Menstrual irregularities were almost the rule in women treated with testosterone propionate: these consisted of simple changes in the amount of the flow, its duration, and the length of the interval, and amenorrhea of shorter or longer duration.

In women past forty, the onset of the menopause is hastened and frequently occurs a few months after the commencement of the treatment. The amenorrhea observed after treatment is of no importance, not even in young women, as compared to the cancer. If the amenorrhea is accompanied by general and unpleasant phenomena (vomiting, dizziness, circulatory troubles), the dose must be reduced or, in serious cases, treatment must even be interrupted for some time to permit the patient's normal state of health to return. However, there are certain cases which are very malignant (diffuse carcinoma) in which the high doses must be maintained by all means.

The use of testosterone after the menopause seems absurd at first. However, one must realize that even in elderly women suffering from cystic mastopathia, estrogen is found in the breast.

As to the dosage to be used, the following points have to be considered: (1) histologic grade of malignancy, (2) clinical stage, (3) age, (4) menstrual cycle, (5) biotype. Except for the first two the others are of secondary importance.

A proper dosage can be established approximately by starting with a minimum of 25 milligrams of testosterone propionate per week and raising it to a maximum of 175 milligrams per week. Within these limits the dose may be determined according to the development of the case and the reactions of the patient.

Patients with diffuse carcinoma (grade IV of histologic malignancy) should usually get the maximum dose of 175 milligrams per week, no matter what the age of the patient. Neither amenorrhea nor signs of virilization observed in young women should prohibit the giving of high doses, since the extreme malignancy of these tumors justifies any secondary disturbances. The dose of 175 milligrams should be maintained during the first year. Thereafter it can be reduced to 100 milligrams during the second year, to 75 milligrams during the third and fourth, and to 50 milligrams from the fifth year on. Treatment for a 5 year period appears not to give a guaranteed protection for the future and it appears justifiable to advise continuing the treatment indefinitely just as insulin is given in diabetes.

This recommendation is based on observations in Cases 40039, 40117, 41221, and 43044, the results of which were unsatisfactory as compared with 2 other Cases 41056 and 41317, (not described in this article), in which no recurrences occurred.

In cases of carcinoma solidum, grade III of histologic malignancy, the average weekly dose should be 75 to 100 milligrams during the first year, depending on whether there are axillary metastases. The age of the patient does not seem to justify a reduction of dose. The dose of testosterone propionate can be reduced or even interrupted when signs of virilization appear, or when a prolonged amenorrhea is accompanied by general unpleasant symptoms. As the years go on, the dosage can be reduced slowly, but a minimum weekly dose of 25 milligrams should be maintained.

In cases of carcinoma adenomatosum, grade II of histologic malignancy, the dosage depends on the presence of axillary metastases. If such are present, the dose should be 75 milligrams, but otherwise, 50 milligrams per week during the first year. In cases without axillary metastases, the dosage can be adjusted for young women according to any secondary symptoms, such as virilization and amenorrhea, observed during the treatment.

In cases of adenoma malignum, grade I of histologic malignancy, there is no need for doses higher than 25 milligrams per week. If there is mastopathia of the remaining breast and persistence of mastodynia after operation, the androgen therapy often brings worthwhile results. The surgical statistics of cases with grade I carcinoma show 100 per cent favorable results without any other treatment

and it does not seem necessary to prolong the treatment with testosterone propionate beyond the 1 year period.

CONCLUSIONS

1. The relationship between hormonal mastopathia and mammary cancer, the influence of estrogens in the occurrence of this tumor, and the biologic antagonism between androgenic and estrogenic hormones justify the use of testosterone propionate in the prophylaxis of mammary cancer after operation.

2. The results obtained in this indication as gauged by the survivals after 3, 4, and 5 years are about 100 per cent better than those observed after operation only. This fact indicates that testosterone propionate exercises a protective or prophylactic action against recurrences of surgically treated mammary cancer.

3. Very high doses of testosterone propionate, up to 175 milligrams per week, may and should be used after operations for mammary cancer, and this treatment should be continued through many years. The principal criterion for the selection of the dosage is the grade of histologic malignancy of the tumor.

4. The side effects following this therapy are of secondary importance. They consist of signs of virilization which occur almost exclusively in young women—at a rate of 50 per cent—and of disturbances of menstruation, even including amenorrhea, occurring in almost all patients.

5. In patients between 40 and 50 years of age who are still menstruating, early cessation of menstruation is often observed.

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RÔLE OF THE DECOMPENSATORY REACTIONS OF PERIPHERAL BLOOD VESSELS IN TOURNIQUET SHOCK

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EVIDENCE that some factor other than fluid loss plays a significant rôle in traumatic shock is clearly indicated by microscopic observation of specific vascular reactions concerned with the peripheral distribution of blood (5). The method employed in these observations (4) is unique in distinguishing the direct compensatory effects of fluid loss from those of the other so called decompensatory or toxemic factor. Fluid loss was found to be accompanied by an increase in the frequency and amplitude of the intermittent constrictor activity (vasomotion) of the terminal arterioles and precapillary sphincters and a hyperreactivity of these vessels to epinephrine, whereas fatal traumatic shock was found to be attended, during the latter half of the syndrome, by a progressive elimination of the vasomotion of these terminal vessels and a hyporeactivity to epinephrine.

The purpose of this investigation is to determine whether in tourniquet shock, this second, decompensatory factor always appears subsequent to fluid loss or whether it may be regarded as a primary factor which normally follows, but may be independent of fluid loss.

In these experiments a variety of tourniquet procedures, including taping of the tourniquet limbs, was used in order to ascertain to what extent it was possible to diminish, in the syndrome, one or the other of the two sets of reactions. It was found that the tendency could be shifted markedly in one or the other direction, but that it was difficult to eliminate either factor completely.

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This paper constitutes the eighth of a series of studies on experimentally induced shock. The first study is listed as (4), the third as (7), the fourth as (19), the fifth as (18), the sixth as (5), and the seventh as (17) in the bibliography of the present paper. The second study, on the Noble-Collip drum method of producing trauma, appeared in *Am. J. Physiol.*; 1943, 139: 123.

The procedure employed in these investigations, viz., the use of directly comparable endpoints through direct observations on the terminal vessels and their responsiveness to epinephrine, makes it possible to eliminate the disturbing effects of the variations exhibited by individual animals and to obtain reasonably consistent, semiquantitative results without resorting to statistical methods. Furthermore, it was possible to determine with considerable accuracy the changes in vascular reactions during the course of each individual shock experiment. These experiments suggest the advisability of using different procedures in the treatment of various forms and stages of shock.

MATERIAL AND METHODS

Shock was induced by a variety of tourniquet procedures in dogs, cats, and rabbits, anesthetized by the intravenous injection of sodium pentobarbital, 30 milligrams per kilogram of body weight.

Complete tourniquet occlusion of both arterial and venous circulation was obtained by means of a length of ¼ inch gum rubber tubing tightly wrapped three times, as high as possible, around a hind limb. This was done on one and two hind limbs for periods varying from 4 to 15 hours. During this period, supplementary pentobarbital injections were given, in minimal amounts never exceeding 10 milligrams per kilogram, to quiet the animal. In some of the complete tourniquet experiments the legs were taped to minimize the subsequent swelling on release of the tourniquets.

About 2 hours before release of the tourniquets the dogs were prepared for microscopic observation of either the omentum or the mesentery. Pentobarbital (5 to 10 mgm./kgm. body weight) was administered and, half an hour later, the omentum was exteriorized according to a technique previously described (Chambers and Zweifach, 4) and maintained

at body temperature by a constant drip of warm gelatin Ringer solution. The mesentery was exteriorized into a transparent chamber according to a technique previously described (Zintel) for the rabbit and modified for the dog by Page and Abell (12). In the present study an improvement was introduced by placing the preparation and the microscope in a constant temperature box, maintained at 37 degrees C. The arterial blood pressure was routinely recorded by cannulating the carotid following exteriorization of the tissue.

In the complete tourniquet experiments, in which swelling of the limb during the tourniquet occlusion is negligible, the microscopic observations were routinely made just prior to and after release of the tourniquet. In a few cases, observations were made during the application of the tourniquet and no significant changes were detected.

In the venous tourniquet experiments an appreciable swelling of the occluded limb always developed within a few minutes after application of the tourniquet. For this reason, the microscopic observations were begun previous to the tying of the tourniquets.

The venous tourniquet experiments were performed principally on the cat, by use of the exteriorized mesentery. Control observations were made on the mesenteric vessels and the tourniquet cords were then tied to occlude only the venous circulation of the limbs. In every case the presence of a pulse in the femoral artery was determined by palpation. In some of the experiments, the femoral veins were also exposed and occluded with a small serrefine clamp. Venous tourniquets on 1, 2, and 4 limbs were applied for periods of 3 to 6 hours.

Hematocrits were determined by the Van Allen method on 0.5 cubic centimeter of blood withdrawn at approximately 1 hour intervals. An indication of the fluid loss into the injured limb was obtained by periodically measuring the circumference of the leg just below the line of the tourniquet application.

Observations of the blood vessels were recorded under the following headings: (1) caliber of vessels, (2) rate and extent of blood flow, (3) presence of periodic, intermittent caliber changes in terminal muscular vessels (vasomotion), (4) response of terminal vessels to epinephrine, and (5) degree of pooling and stagnation of the blood.

Measurements were made with an ocular micrometer at a magnification of 86 diameters (oc., 20×; obj., 2.3×). In the omentum the measured arteries ranged in caliber from 20 to 150 micra and the veins from 25 to 250 micra. In the mesentery vessels of larger caliber were measured, up to 700 micra for the arteries and 950 micra for the veins. Capillaries and terminal arterioles were observed in both the omentum and mesentery under a magnification of 280.

The blood samples were drawn from the jugular vein throughout the syndrome whenever a change in reactivity was recorded in the mesenteric vessels under observation. The serum from these blood samples was tested for the presence of active humoral principles by the rat mesoappendix test previously described (6). For these tests, normal 100 to 160 gram rats were anesthetized with 3 to 4 milligrams of sodium pentobarbital and the mesoappendix was exposed for microscopic observation. The blood pressure was recorded by an indirect method previously described (Duncan, Hyman, and Chambers). The effect of the injection into the rat of 0.5 cubic centimeter of shock serum on blood pressure, rate of blood flow, vasomotion, and response of the terminal arterioles to topically applied epinephrine was determined.

Samples were recorded as vasoexcitor (hyperreactive) when their injection induced an increased reactivity of the terminal arterioles to epinephrine. Many of the samples also accelerated vasomotion and raised the blood pressure 10 to 20 millimeters of mercury. Blood samples were recorded as vasodepressor (hyporeactive) when they brought about a decreased response to epinephrine. They also frequently blocked vasomotion and lowered the blood pressure. Samples were recorded as neutral when they brought about no change in the criteria studied except for a transitory speeding of blood flow due to the fluid introduced by the injection.

Vasomotion, a term previously employed, designates the periodic caliber changes which normally occur in the terminal arterioles at

TABLE I.—COMPILATION OF 27 FATAL CASES OF A TOTAL OF 37 ANIMALS STUDIED (24 COMPLETE AND 13 VENOUS TOURNIQUETS). DATA ARE ARRANGED INTO THREE CATEGORIES ACCORDING TO RELATIVE PREDOMINANCE OF HYPERREACTIVE OR HYPOREACTIVE VASCULAR CHANGES

Animal	Type of tourniquet	Duration of tourniquet hours	No. of animals	Survival time* hours	Hematocrit		Vascular reactivity				Ratio of hyper/ hypo. duration
							Hyper		Hypo		
					Control per cent	Final per cent	Time* of appear. hours	Duration hours	Time* of appear. hours	Duration hours	
A. Vascular hyperreactivity predominates:											
Dog	Venous, 4 legs	4	1	3.5	36	51	at 0.3	2.7	—	—	—
Dog	Complete, 2 legs	4 to 5.5	2	4.0	38	48	at 0.35	3.0	—	—	—
Cat	Venous, 2 legs	4.5	2	4.0	39	50	at 0.55	2.9	at 3.7	0.3	8.2 : 1
Dog	Complete, 2 legs	6 to 7	1	3.2	44	63	at 0 5	2.0	at 2.5	0 4	4.8 : 1
B. Vascular hyperreactivity and hyporeactivity both prominent:											
Cat	Venous, 2 legs	5.0	2	7 to 8	39	46	at 0.3	3.1	at 5.5	1.5	2.0 : 1
Cat	Venous, 1 leg	6.0	1	5.5	33	39	at 0.6	2.0	at 4.5	1.1	1.8 : 1
Dog	Complete, 2 legs	6 to 7	5	5 to 6	42	58	at 0.5	2.0	at 3.5	2.5	1.0 : 1.3
Cat	Complete, 1 leg	5.0	1	4.5	34	42	at 0.45	1.5	at 2.5	2.0	1.0 : 1.3
Dog	Complete, 2 legs (taped)	6 to 7	2	7.0	45	54	at 0.6	1.75	at 3.0	2.75	1.0 : 1.5
C. Vascular hyporeactivity predominates:											
Cat	Venous, 1 leg	6.0	1	5.0	34	41	at 0.6	1.5	at 3.0	2.0	1.0 : 1.5
Dog	Complete, 2 legs (taped)	6 to 7	2	4.5 to 5	41	45	at 0.6	1.25	at 3.0	2.0	1.0 : 1.6
Dog	Complete, 2 legs	6 to 7	2	3 to 4	41	49	at 0.6	1.0	at 1.5	2.5	1.0 : 2.5
Dog	Complete, 2 legs	10 to 12	2	2.5 to 3	40	43	at 0.7	0.5	at 1.0	2.0	1.0 : 4.8
Rabbit	Complete, 1 leg	6.5	1	4.5	38	42	at 0.3	0.8	at 2.1	2.3	1.0 : 9
Cat	Complete, 1 leg	6.0	2	3.5	40	47	at 0.5	0.3	at 1.0	2.5	1.0 : 10

*Time, in complete tourniquet experiments, refers to time after release of tourniquets and, in venous experiments, to time after tying of cords.

varying intervals and which are of importance in regulating the distribution of blood to the capillary bed. During the shock syndrome the vasomotion generally becomes augmented and then depressed. By "augmented" is meant a condition in which the frequency of periodic contraction-relaxation cycles is increased, and in which the constrictor phase becomes increasingly predominant (for details see Chambers and Zweifach, 4). By "decreased" is meant a condition in which the frequency of the contraction-relaxation cycle is diminished below normal and in which the dilator phase becomes progressively predominant. A stage is finally reached in which the vasomotion ceases with the terminal arterioles remaining in the relaxed state.

The reaction of the terminal arterioles to the topical application of varying concentrations of epinephrine was determined according to a technique previously described (Chambers and Zweifach, 4). The minimal effective concentration of epinephrine was that which produced a temporary contraction of the terminal arterioles so as to slow or interrupt the capillary flow for 10 to 20 seconds. This concentration was recorded as the minimal effective concentration for a given case.

Autopsies were routinely made on the viscera and the limbs.

EXPERIMENTAL OBSERVATIONS

A total of 37 animals—dogs, cats, and rabbits (see Table I)—were studied. Of these 24 developed fatal shock. The data are presented on the basis of the circulatory changes observed, rather than of a statistical analysis of each type of tourniquet procedure. About 95 rats were used for the mesoappendix tests of blood samples.

General survey of circulatory changes. A study of the normal capillary circulation in the omen-

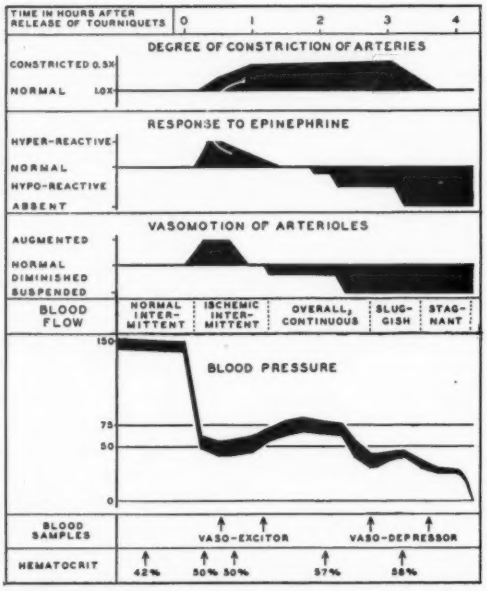

Chart 1. Protocol illustrating vascular changes typical of intermediate category, in which both hyperreactivity and hyporeactivity are prominent. Dog No. 7, male, weight 8.5 kilograms, sodium pentobarbital, 30 milligrams per kilogram body weight, subjected to complete tourniquet of 2 hind limbs for 6 to 7 hours. "Degree of constriction" and "Response to epinephrine" are expressed as multiples or fractions of the normal. Deviations are charted above or below the normal base line. Vasomotion (intermittent arteriolar caliber changes) is expressed as the proportion of time that constrictor phase persists in relation to relaxation phase. When "augmented" the constrictor phase predominates and vice versa when "diminished." When "suspended" the relaxation phase persists.

tum and mesentery has made possible the selection of several well defined vascular reactions which have been found to be affected consistently in traumatic shock (5, 18). The reactions are specific enough to distinguish the circulatory effects of fluid loss *per se* from those of other conditions in the shock syndrome.

The stages in tourniquet shock which lead to circulatory collapse can be resolved into two all inclusive categories. This was always found to be the case, regardless of the variations in the experimental procedure or of complications introduced by the individual variations in the natural resistance of the experimental animals.

The two categories have been designated as hyperreactive and hyporeactive. One is concerned with compensatory vasoconstrictor reactions to fluid loss and the other with decompensatory reactions associated with the deterioration of the physiological responses of the terminal blood vessels. The interplay of these two groups of reactions, as to extent, duration, and suspension of one or the other, appears to account for all the variations observed.

The animals were classified under three general patterns of vascular response on the basis of the relative duration and intensity of hyperreactivity and hyporeactivity. This is indicated in Table I under A, B and C.

In one set of animals, A, the hyperreactive pattern was emphasized. It developed early and persisted during the greater part of the syndrome; hyporeactivity appearing only during the terminal minutes or not at all. The hyperreactive circulation was characterized by vasoconstriction, capillary ischemia, augmented vasomotion, and heightened responsiveness to epinephrine. Death occurred with marked peripheral ischemia.

In the second set of animals, C, the hyporeactive pattern was emphasized. It appeared early, was of long duration, and was preceded by a brief hyperreactive state or almost by none. The hyporeactive circulation was characterized by a progressive slowing and eventual suspension of vasomotion, filling of the capillaries and of the collecting venules with increasing amounts of blood, a subnormal responsiveness to epinephrine and, finally, a partial relaxation, first of the terminal arterioles and later of the arteries and veins. Death occurred with considerable congestion of the capillaries and venules.

In the third set of animals, B, intermediate between the above extremes, hyperreactivity and hyporeactive patterns were equally prominent. There was considerable variability in the extent to which hyporeactivity progressed in each animal, apparently depending in large part upon the degree to which the blood flow had already been curtailed by the initial hyperreactivity.

Description of the circulatory responses. Complete tourniquet occlusion of the circulation in two hind limbs was carried out for periods of 4 to 15 hours on dogs under pentobarbital anesthesia (Table I). The largest number of ex-

TABLE II.—CHANGES IN CALIBER OF LARGE BLOOD VESSELS IN OMENTUM AND MESENTERY DURING FATAL TOURNIQUET SHOCK

Time* per cent	Hyperreactive category				Intermediate category				Hyporeactive category			
	A_1	V_1	A_2	V_2	A_1	V_1	A_2	V_2	A_1	V_1	A_2	V_2
0	90	135	24	30	82	97	67	75	125	210	43	64
25	66	120	21	24	52	87	52	72	110	210	43	64
50	60	105	15	18	45	102	60	78	115	225	40	66
70	54	93	9	12	60	105	60	78	125	230	43	69
80	45	90	9	12	73	105	64	81	125	230	47	71
90	60	105	18	24	82	108	67	90	125	230	47	73
95	72	117	21	24	82	115	68	92	125	235	48	75
100	60	104	16	20	75	110	60	84	108	221	39	67

A_1 arteries; A_2, arterioles; V_1 and V_2, their corresponding veins and venules. Diameters of vessels are in micra, the figures being taken from typical experiments in each category.

*Time is indicated as percentage of total posttourniquet period. Terminal vasoconstriction, during agonal death period, is indicated at 100 per cent.

periments were with 6 to 7 hour tourniquets in which fatal shock occurred in a high percentage of the cases.

Out of a total of 8 dogs in the group in which complete tourniquet occlusion of *2 hind limbs for 6 to 7 hours* was carried out, 1 dog showed hyperreactivity which persisted through the greater part of the syndrome, 2 dogs showed a comparatively short period of hyperreactivity followed by a pronounced hyporeactive stage, and 5 showed an intermediate condition in which the periods of hyperreactivity and hyporeactivity were more nearly equal. The intermediate constituted the largest group and is discussed first.

The vascular reactions characteristic of the animals in the *intermediate category* are shown in Chart 1, which is a diagrammatic presentation of the protocol data of a typical member. The initial change following release of the tourniquets was an abrupt lowering of blood pressure which occurred within 1 to 3 minutes after release of the tourniquet, before any significant swelling of the leg could be detected. There was no marked change in the caliber of the omental blood vessels and only a moderate slowing of the flow in the peripheral vessels.

Within 10 to 15 minutes, the swelling of the legs became appreciable and reached a maximum within 1 to 2 hours, the circumference of the limbs increasing by 16 to 19 per cent over the control. During this period of swelling, the larger vessels in the omentum, especially the arteries and larger arterioles, narrowed to about half of their original caliber (Table II). At about the same time, the intermittent caliber changes of the terminal arterioles became more frequent and maintained the constricted state for a relatively longer proportion of the total period. This was especially pronounced in the precapillary junctions, sphincter-like arrangements of muscle about the proximal end of the side branches leading from the terminal arterioles into the capillaries. During this period of ischemia, a continuous circulation coursed only through the most direct channels from artery to vein. The hyperreactivity of the terminal blood vessels at this stage was further indicated by their response to dilutions of epinephrine averaging one part in 10 to 12 million as compared with control values of one part in 3 to 4 million.

Blood samples, taken during the hyperreactive period, were found to be markedly vasoexcitor when tested on the terminal blood vessels in the mesoappendix of normal rats. They produced, on intravenous injection in the test animals, three or four times the epinephrine reactivity, a transient ischemia of the capillary bed and, in some instances, a blood pressure rise of 15 to 20 millimeters of mercury. The hyperreactive effects on the rat circulation persisted for 20 to 35 minutes.

During the ensuing 1 to 2 hours in the shocked dog there appeared a progressive slowing of the blood flow through the omental vessels, especially in the venules draining the capillary bed and in the small veins.

The blood pressure, which at this time varied in different animals from 55 to 75 millimeters of mercury, showed no significant change and, in some cases, even tended to rise. Hemoconcentration of the blood was observed, the hematocrit rising from a control value of 40 to 50 per cent to a value of 57 to 62 per cent. This tendency toward hemoconcentration was also detected by the concentrated appearance of the blood in the peripheral vessels.

The vasoconstrictor and hyperreactive aspect of the syndrome began to shift toward vascular relaxation and hyporeactivity about 1.5 to 2 hours after the tourniquets had been released. The initial change in this direction was a decrease and subsequent disappearance of vasomotion. At about the same time the hyperreactivity to epinephrine began to fall off. This downward trend progressed at a somewhat slower rate than did the deterioration of vasomotion so that the epinephrine reactivity did not actually become subnormal until some 30 to 90 minutes after vasomotion had fallen markedly below normal. At about the time that the epinephrine reactivity became subnormal, the larger arteries and arterioles began to relax, in some instances returning to their control diameters. Blood samples taken at this stage were found to be vasodepressor. They produced in the test rat circulation a diminished response to epinephrine, a slowing of flow especially noticeable in the venules and in some instances a fall in blood pressure of about 30 to 40 millimeters of mercury. Samples taken about 1 hour earlier, during the period in which the shift toward hyporeactivity in the omental or mesenteric circulation was becoming apparent, were found in most cases to give no demonstrable effect. Some blood samples taken during this transitional period produced in the rat mesoappendix first a brief hyperreaction followed by a hyporeaction, suggesting the presence in the sample of both hyperreactive and hyporeactive principles which exert their effects in different time periods. This conclusion is supported by unpublished data on similar intermediate or neutral sera obtained in graded hemorrhage experiments which, by chemical means, were separated into fractions exerting respectively hyperreactive and hyporeactive effects.

It is important to note that the decompensatory changes in the shocked animals occurred while the blood flow through the omentum or mesentery was still fair. At this stage, the essential difference between animals that recovered and those that ultimately died of shock was the development of hyporeactivity in the latter. Those animals that survived maintained a reduced level of blood flow for about 1 to 2 hours and then progressively began to improve. In the cases which resulted fatally the blood flow became increasingly sluggish after the hyporeactive vascular changes had taken place. The deterioration in peripheral blood-flow occurred in two stages. First, with the gradual suspension of intermittent constriction of the terminal arterioles, more capillaries exhibited a continuous but somewhat slowed flow. Second, with the complete suspension of vasomotion and a partial relaxation of the larger arterioles, the flow on the venous side of the circulation became increasingly sluggish, especially in the collecting venules. At this stage the blood pressure began to fall slowly, losing about 2 to 3 millimeters of mercury every 10 minutes. This type of sluggish circulation persisted for about an hour, during which the terminal arterioles became almost completely unresponsive to epinephrine and the arteries and arterioles underwent further partial relaxation. Many of the small venules became distended. Considerable stagnation and stasis were present throughout the capillary bed. The blood pressure reached a level of 28 to 40 millimeters of mercury. The final 40 to 50 minutes of the syndrome were characterized by an almost complete absence of blood flow.

Blood samples taken during the final 60 minutes of the syndrome were consistently hyporeactive. In the test rat they not only depressed epinephrine reactivity and vasomotion, but usually lowered the blood pressure to a considerable extent, in some cases by as much as 50 to 60 millimeters of mercury.

About 10 to 15 minutes before death, when the shocked animal was showing marked respiratory difficulty, there took place an intense constriction of the larger arteries and their terminal branches. This did not affect the peripheral flow, which had already been stag-

nant for some time. The constriction persisted until death and was present at autopsy. Thus, the consistent finds of vasoconstriction at autopsy bear no relation to the progressive changes observed during the stages leading to collapse.

At autopsy the liver and gastrointestinal tract were moderately congested. The serosal surface of the gut was purplish. The mucosa was congested throughout, and the duodenal portion was frequently hemorrhagic. The cut surface of the kidney appeared ischemic. The adrenals were markedly congested, especially in the medulla.

In the 1 dog which came under the *hyperreactive category* the hind limbs showed a greater degree of swelling than did those in other members of the 6 to 7 hour tourniquet series, the increase in circumference being about 24 to 25 per cent above the control. Vasoconstriction of the arterial vessels was marked (Table II) and was accompanied by widespread ischemia. Within 10 minutes after release of the tourniquets, vasomotion of the terminal arterioles in the omentum became more rapid, with the contraction phase of the cycle persisting 4 to 5 times longer than the relaxation phase. This augmented condition lasted for about 3 hours and, at the peak, the terminal arterioles responded to one part in 16 million of epinephrine, as compared with the initial control response to one part in 4 million. However, in contrast to the conditions in the intermediate group, the blood flow through the bed was markedly curtailed by the extreme vasoconstriction and hyperreactivity. This condition persisted for slightly more than 2 hours, when an abrupt transition into a hyporeactive state became apparent.

The differences between the hyperreactive and intermediate categories are strikingly brought out in Chart 2, in which the three categories of vascular response are compared with one another. About 30 minutes before death vasomotion became less pronounced, epinephrine reactivity fell sharply to subnormal levels and arterial relaxation occurred. The epinephrine reactivity, although continuously falling from its hyperreactive peak, never became hyporeactive to the extent of complete

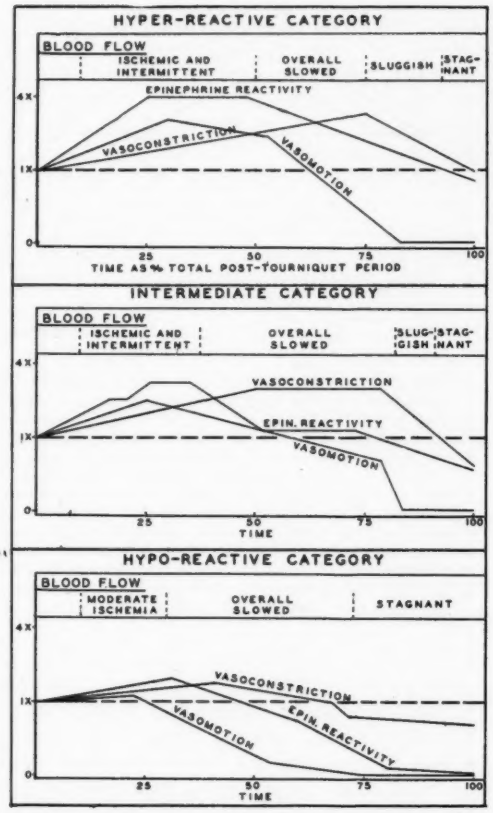

Chart 2. Comparison of significant changes in vascular reactions during fatal tourniquet experiments. Data represent averages compiled from 27 animals, 8 in hyperreactive, 10 in intermediate and 9 in hyporeactive category. Normal value is expressed as 1×; the changes during syndrome, as multiples or fractions of normal value.

unresponsiveness to epinephrine. A constrictor response to 1 part in 2 million (control value being 1 part in 4 million) was obtained at 15 minutes before death. There was some pooling of blood and stagnation in the venules and in the capillaries leading into them.

At the time of circulatory collapse the capillary bed was still ischemic when compared with the control but contained more blood than had been present during the early hyperreactive stage.

In the hyporeactive category were 2 dogs which underwent collapse with only moderate vasoconstriction and a considerable pooling of

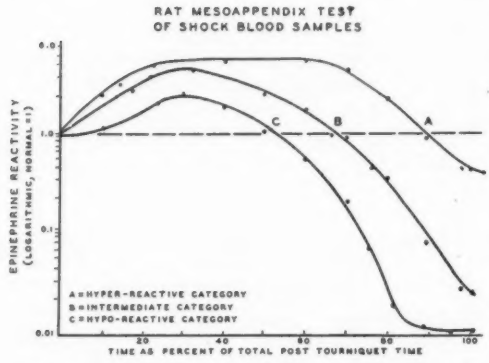

Chart 3. Reactivity of shock blood samples taken at different times during the syndrome in fatal tourniquet experiments. The three categories: hyperreactive *C*, intermediate *B*, and hyporeactive *A*, are charted separately, using a logarithmic scale to plot the concentration of epinephrine at which a standard constrictor response was obtained. Control epinephrine value is expressed as 1.0 (broken horizontal line). Changes from normal are expressed as multiples or fractions of control value; above base line, vasoexcitor; below base line, vasodepressor. The data are based on rat mesoappendix tests of 95 separate samples obtained at intervals during the shock syndrome. On the average 3 to 4 samples were used from each of 27 fatal experiments.

blood in the capillary bed (Table I). The injured limbs swelled only slightly after release of the tourniquets, the circumference increasing about 10 per cent over that of the control value. The initial fall in blood pressure was as great as in the preceding experiments, but the pressure never leveled off and continued to fall throughout.

Vasoconstriction did not appear until about 30 to 40 minutes after release of the tourniquets. It was only moderate in character, the narrowing being about 12 to 16 per cent in the arteries and arterioles as compared with the 50 to 60 per cent usually observed in other 2 limb tourniquet experiments. Vasomotion gradually disappeared without ever having become more rapid than normal. The response to epinephrine rose slightly from the control level of about 1 part in 3 million to 1 part in 5 million and remained slightly hyperreactive for only 15 to 20 minutes. Peripheral circulation never became ischemic. An active flow persisted in all the capillaries during the first hour, then progressively slowed until it became almost stagnant as early as about 2 hours after release of the tourniquets. At this time, no vasomotion was present, the terminal arterioles were completely unresponsive to epinephrine and were actually dilated. During this latter period, the arteries relaxed to their control diameters, followed by a slight dilatation of some of the larger arterioles (Table II). The venules contained only stagnant blood and, in some areas, a backflow into the capillary bed was present. Many of the capillaries also contained considerable amounts of stagnant blood. About 15 minutes before death, the flow in the arteries had become pulsatile and no forward movement existed in the capillary bed.

The hematocrit showed only a moderate increase of about 18 to 20 per cent above the control in these 2 dogs.

Blood samples were vasoexcitor only during the first 25 to 35 minutes following the release of the tourniquets, and became increasingly vasodepressor from then on. A blood sample from one of the dogs taken 20 minutes before death produced in the test rat a hyporeactive response which persisted for over an hour.

The changes in the three categories may be analyzed as follows: The vascular changes occurred in the same relative sequence, despite the variability of the relative lengths of the hyporeactive and hyperreactive periods. Reactions of the larger and smaller blood vessels were always in the same general direction. During the hyperreactive stage, vasoconstriction of the larger blood vessels was accompanied in the terminal blood vessels by its counterpart, an augmented vasomotion and an increased responsiveness to epinephrine. Hyporeactivity appeared first in the terminal blood vessels and subsequently the larger blood vessels showed a similar tendency by their relaxation (Chart 2). In these cases, the disappearance of vasomotion and fall in epinephrine response from its hyperreactive peak occurred while the vasoconstriction of the larger blood vessels still persisted. In the 2 dogs which developed a markedly hyporeactive condition early, the tendency toward relaxation appeared simultaneously in both the larger and terminal blood vessels.

The development of humoral vasoexcitors and vasodepressors closely parallels the vascular changes in the 3 categories of animals.

The gradual appearance of hyporeactivity in the intermediate category, in contrast to the abrupt transition between hyperreactivity and hyporeactivity which occurred early in the extreme hyporeactive category, is well demonstrated in Chart 3.

In conclusion it may be stated that in some experiments hyporeactivity was preceded by vasoconstriction and hemoconcentration. In others hyporeactivity was preceded by vasoconstriction alone and not by any significant change in hemoconcentration. In still others, and this point should be emphasized, hyporeactivity progressively developed without a significant preceding vasoconstriction or hemoconcentration.

In the group in which tourniquets were applied to *2 hind limbs for less than 6 hours*, 1 dog with a 4 hour tourniquet application survived for more than 8 hours after the release of the tourniquet, at which time it was sacrificed. Two dogs to which tourniquets were applied 5 and 5.5 hours died in 6 and 7 hours, respectively, after release of the tourniquet. The circulatory collapse in these 2 fatal cases was of the hyperreactive type, in which hyperreactivity persisted for 4 to 5 hours, and was followed only during the final hour of the syndrome by a gradual deterioration of the peripheral circulation.

The blood samples were hyperreactive during the first 2 hours following release of the tourniquets and then for almost 3 hours remained neutral, i.e., gave no test response. This long neutral or transitional period persisted until about 30 minutes before collapse ensued, a hyporeactive blood sample being obtained in 1 case 30 minutes and in the other 25 minutes before death.

Thus, the shorter duration of tourniquet occlusion favored a hyperreactive type of circulatory collapse. Under these conditions, vasoconstriction was a prominent feature during the phases leading to collapse.

In the group in which tourniquets were applied to *2 hind limbs for more than 7 hours*, 4 experiments were made, in 2 dogs for 10 to 12 hours and in 2 for 15 hours. Both dogs in the 10 to 12 hour tourniquet group died, whereas the 2 dogs in the 15 hour group survived and were sacrificed.

The essential difference between the 2 sets of experiments was the failure of the circulation to return to the limbs which had been occluded for 15 hours. They remained cold, the toe pads did not bleed when incised, and the limbs showed no appreciable swelling. No vasoconstriction was observed in the visceral blood vessels and no change either in vasomotion or epinephrine reactivity was detected. The blood flow through the peripheral vessels remained relatively unchanged for a period of 6 to 7 hours, at which time the animals were sacrificed.

The lethal 10 to 12 hour experiments showed the most marked development of a hyporeactive condition of all the two limb tourniquet experiments. The initial blood pressure drop was not as marked as in all previous experiments, falling from a control value, in 1 instance, of 140 to 80 millimeters of mercury and, in the other, of 150 to 84 millimeters of mercury. Circulatory collapse was obtained in both instances with almost no initial vasoconstriction and with only a very slight increase in hematocrit. Constriction of the larger blood vessels was negligible, and in all instances relaxation occurred within 1 hour after release of the tourniquets. The veins became slightly dilated about the same time that the arteries began to relax. The circulation deteriorated rapidly and showed marked congestion and stagnation in the venules and in the inflowing capillaries.

The blood samples were vasodepressor, in 1 instance, 70 minutes and, in the other, 95 minutes after release of the tourniquets. Hyporeactivity was detected earlier than in any of the other experiments in the present study.

Thus, provided circulation was restored to the damaged limbs, the hyporeactivity became increasingly evident when the period of tourniquet application was in excess of 7 hours.

In a group of 7 dogs *both hind limbs were taped* before tourniquets were tied for a period of 6 to 7 hours. The tape was applied just tightly enough to diminish the swelling which occurs after release of the tourniquets. Only 4 of the 7 dogs died, in contrast to the 6 to 7 hour experiments in which limbs were not taped and all the dogs died. None of the dogs in the series in which the limbs were taped

died with a hyperreactive pattern of vascular response.

The initial fall in blood pressure immediately on release of the tourniquets was very similar to that obtained in experiments in which limbs were not taped. The blood pressure usually fell to the 50 to 70 millimeters of mercury range, irrespective of the ultimate fate of the animal.

In 2 dogs the taping was loose enough to permit some swelling of the leg, and fatal circulatory collapse occurred within 5 hours after release of the tourniquets. Both dogs showed the usual sequence of initial hyperreactive change followed by hyporeactive changes in the omentum and mesentery. In 1 dog, the vasoconstriction of the larger vessels was as marked as in the untaped animal and there was a considerable rise in hematocrit, from 45 per cent to 60 per cent. In the other dog, only a moderate vasoconstriction occurred and the peripheral blood flow remained good for almost 3.5 hours before hyporeactivity ensued.

In 5 of the 7 taping experiments, there was no significant swelling of the damaged limbs. Three of these 5 animals survived and showed no appreciable vasoconstriction, almost no change in hematocrit, and only a moderate slowing of blood flow in the mesentery and omentum. They had a blood pressure of 55 to 65 millimeters throughout the 8 to 10 hours of observation and were then sacrificed.

Two of the 5 dogs died despite the almost complete absence of swelling in the damaged limbs. In these, vasoconstriction was practically negligible, a transient narrowing in caliber appearing only in some of the 50 to 60 micra arterioles. The hematocrit level remained remarkably constant during the period in which the peripheral circulation was deteriorating and then rose slightly during the final 1 to 1.5 hours of the syndrome. There was no restriction in capillary circulation of the type following augmented vasomotion as previously described. Vasomotion was abolished within 1 hour after the release of the tourniquets. The epinephrine response increased to a twofold maximum but did not maintain this peak and fell progressively to subnormal levels. The slowing in blood flow became increasingly evident on the venous side of the peripheral circulation and was followed by a pronounced pooling of blood in the collecting venules and small veins. Death occurred with considerable congestion and stasis in the capillary bed.

Blood samples produced essentially the same sequence of reactions as were found in similar untaping experiments.

In general, the taping was found to permit the maintenance of an adequate visceral circulation for longer periods of time than in untaped animals. This is probably related to the fact that less fluid was lost into the taped limb. All of the dogs whose limbs were taped and tourniquets applied showed, at autopsy, a considerable congestion and hyperemia of the viscera. The gastrointestinal tract, liver, and kidney were especially congested. The mucosal surface of the gut was hemorrhagic, especially in the duodenal region. The kidney appeared distended and on being incised bled freely, in contrast to the ischemic condition usually found in untaped experiments.

In the experiments with *complete tourniquet occlusion of 1 limb*, it was found that fatal shock in dogs could not be induced in periods of 8 to 10.5 hours by this means. The circulatory data for fatal one limb tourniquets were obtained in 3 cats and 1 rabbit, which readily went into fatal shock with 6 to 7 hour 1 limb tourniquets. The microscopic observations were made with the transparent mesenteric chamber technique. The animals died from 2 to 4.5 hours after release of the tourniquets and showed a sequence of vascular changes which was predominantly hyporeactive. Vasoconstriction was moderate and in 2 cases did not appear at all. Circulatory collapse occurred with considerable congestion and stasis through the peripheral vessels.

The vascular reactions following the application of *venous tourniquets* were observed in the mesentery of cats and omentum of dogs. Circulatory changes appeared within a relatively short time after the tying of the cords, whereas with complete tourniquets no significant changes in the peripheral vessels were observed prior to the release of the tourniquets. With complete tourniquets, the few instances in which there occurred an increase in hematocrit and slowing of blood flow prior to release of the tourniquet were probably at-

tributable to the unsatisfactory application of the tourniquets. In the dog it was more difficult than in the cat or rabbit to tie a tourniquet, which was unquestionably complete, without producing considerable trauma under the rubber tourniquets. This difference appeared to be related to the toughness in the dog of the leg musculature in contrast to the soft, flabby muscles of the cat and rabbit.

Venous tourniquets on 4 legs for 3.5 hours and on 2 limbs for 4 hours produced fatal shock characterized by an exaggerated hyperreactive pattern of response. Vasoconstriction appeared within 10 minutes after the cords had been applied and increased progressively until, at the end of 1.5 to 2 hours, the larger arteries were constricted to one-third their original diameters. During the first half of this period the blood pressure was actually 30 to 40 millimeters of mercury higher than the control levels. The capillary circulation was markedly ischemic with a continuous flow only through a few vessels. Vasomotion of the terminal arterioles was pronounced and the constrictor phase was so intense as to interrupt the flow for as long as 2 to 3 minutes. The blood pressure then began to fall and over a period of an hour had shown a drop of over 100 millimeters of mercury. During this period the flow in the venules and small veins became considerably slowed and finally intermittent. Of the 3 animals (Table I) which died with this type of vascular change, 1 maintained the constricted condition until about 20 minutes before the tourniquets were untied, upon which relaxation of the constricted condition occurred. In the 2 other animals, 1 underwent relaxation about 10 minutes after the tourniquets were released and 1 died within 35 minutes after release of the tourniquets, with no relaxation. Death occurred in all 3 animals with an ischemic peripheral circulation. Blood samples were vasoexcitor throughout the syndrome.

Venous occlusion of 2 limbs for 5 hours (2 cats) and 1 limb for 6 hours (3 cats) produced fatal shock in 4 of the 5 cases. The circulatory response showed a hyperreactive state during the initial 3 to 4 hours in which the tourniquets were left in place which was followed by a subsequent hyporeactive pattern. In the 2 animals subjected to fatal 1 limb 6 hour tourniquets, the vascular response showed a pronounced hyporeactive condition in the final hour of the syndrome. Blood samples were moderately vasodepressor only during the final 40 to 45 minutes prior to death.

EVALUATION OF STUDY

The establishment of definitive criteria by microscopic observations of the vessels directly concerned with circulatory collapse permitted a critical analysis of the factors underlying the shock syndrome. The tourniquet shock syndrome could be resolved into two sets of reactions, compensatory and decompensatory, which could be distinguished by specific vascular changes in the omentum and mesentery involving, on the one hand, the intensity of vasoconstrictor changes and, on the other, the interaction of hyperreactivity as against hyporeactivity in the peripheral circulation. Both the compensatory and the decompensatory changes contributed to the development of the markedly reduced blood flow characteristic of fatal shock. The former induced a reduction in blood flow through a widespread vasoconstriction and hyperreactivity of the terminal blood vessels, while the latter impaired the peripheral circulation through interference with the intermittent constriction of the terminal arterioles and precapillary sphincters which regulate the extent and distribution of blood flow in the capillary bed.

It is generally agreed that the circulatory failure characteristic of traumatic shock is essentially initiated by a reduced blood volume (Blalock; Wiggers; Kety and Pope). Most of the recent work has stressed fluid loss into the traumatized tissue as the primary factor responsible for the fatal reduction in blood volume. The present study on tourniquet shock lays emphasis on the decompensatory changes in the terminal vessels as playing an important rôle in reducing the circulating blood volume to critical, shock levels.

In the omentum and mesentery, the onset of decompensation is marked by a progressive diminution of the intermittent constriction and a relaxation of the terminal arterioles and precapillaries until spontaneous caliber changes are no longer detectable. The primary effect

is to permit active circulation through a larger number of capillaries than hitherto. At about the same time, the responsiveness to epinephrine begins to fall from its hypernormal peak and ultimately reaches subnormal levels. During this period the muscular venules become completely relaxed. The net effect is a progressive slowing of the peripheral blood flow, especially on the venous side. Later, through relaxation also of the larger vessels, there develops a further discrepancy between the available blood volume and the capacity of the vascular bed. The resultant further slowing of flow occasions pooling and stagnation in the capillary bed, especially in the collecting venules—factors which serve to reduce the circulating blood volume still further and eventually lead to circulatory collapse.

Similar pooling and stagnation of blood in the peripheral circulation during hemorrhagic shock have been recently reported on the basis of direct visual observation (Zweifach, Lee, Hyman, and Chambers, 18; Abell and Page, 13) and indirectly through studies on the distribution of "tagged" radioactive isotopes (Fine, Seligman, and Frank).

Compensatory vascular reactions were found to be related to the degree of fluid loss and decompensatory reactions to the development of so called toxemic factors. Previous experiments with hemorrhage (19) have indicated that the augmentation of peripheral vascular reactivity (hyperreactive state) was related to the extravascular loss of fluid. In the present tourniquet experiments, the same type of hyperreactivity appeared during the period in which the damaged limbs were swelling, being most pronounced in animals showing the greatest degree of swelling. Hyperreactivity was likewise magnified when the number of limbs subjected to tourniquet occlusion was increased, presumably as a result of the greater amount of fluid loss because of the larger mass of tissue involved. By contrast, hyperactivity was least prominent when the swelling of the limbs was negligible. The direct relationship between fluid loss and hyperreactivity was strikingly brought out in taping experiments, where curtailment of fluid accumulation in the damaged limbs resulted in the almost complete suppression of hyperreactivity.

In the untaped animals in which both hyperreactivity and hyporeactivity developed, the hyperreactive vascular changes attending fluid loss always appeared, as observed in the omentum and mesentery, during the early part of the syndrome. The subsequent appearance of decompensatory or hyporeactive vascular reactions could not be ascribed to fluid loss *per se*.

Previous experiments on hemorrhagic shock (16, 17) have shown the marked influence of the anesthetic agent in favoring the development of hyporeactive vascular changes. Pentobarbital sodium was among the anesthetic agents which, in the presence of a curtailed peripheral circulation, was found to predispose the animal to the elaboration of vasodepressors. In the present experiments no attempt was made to vary this factor, pentobarbital being the anesthetic agent used throughout. Care was taken that the amount of anesthetic was minimal, none being administered after the omentum or mesentery was exteriorized.

With uncomplicated hemorrhage of animals anesthetized with pentobarbital (19), hyperreactive vascular responses were obtained to within a few minutes of death. Hyporeactivity was not produced by hemorrhage procedures unless the animal was maintained artificially for a prolonged period with a severely curtailed peripheral blood flow by repeated small infusions. In tourniquet shock, no similar reduction in blood flow, as observed in the omentum and mesentery, preceded the development of hyporeactivity, and the shift toward decompensation appeared while the peripheral blood flow was still good. It appears, therefore, that the hyporeactivity in tourniquet experiments must be related to processes occurring remote from the omentum or mesentery, presumably in the traumatized limbs. Strong support for such a toxemic factor is the demonstration of a vasodepressor humoral principle in blood from shocked animals withdrawn at the time that the omentum and mesentery show hyporeactive vascular changes. The occurrence of two oppositely acting humoral principles, each corresponding to the circulatory condition at the time of withdrawal, is significant. Thus a vasoexcitor principle

could be detected in the blood during the period in which the reactions attending fluid loss predominate while a vasodepressor principle could be detected at the time when the visceral vessels become hyporeactive. The terms vasoexcitor and vasodepressor refer to the over-all accelerating or inhibiting effect on the reactivity of the terminal blood vessels and do not refer to grosser phenomena, such as blood pressure or arterial dilatation. The fact that both the larger and small blood vessels ultimately exhibit the same type of response, although at different times, seems to indicate that the hyperreactive and hyporeactive principles affect both sets of vessels.

Adherents to the fluid loss hypothesis point out that, during shock, changes appear in almost all the metabolic constituents of the blood, and they have claimed that it is difficult to relate the ensuing circulatory collapse to any of these factors. However, it should be emphasized that in our experiments the intravenous administration of relatively small amounts of serum from the shocked animal always reproduced in test rats precise vascular reactions characteristic of the circulation in the shock host. The fivefold to tenfold dilution of the test sample in the blood stream of the recipient makes it highly improbable that the specific vascular changes considered in the present study could be accounted for by general changes in blood or tissue metabolites referable to stagnant anoxia. The appearance of a humoral hyporeactive principle consistently at the time when the vascular reactions become hyporeactive points to its being related to a particular rather than to a broad type of metabolic change. Petechial hemorrhages are not produced by the hyporeactive principle either in the shocked animals or in animals receiving injections of shock serum. This appears to discount the contention of certain investigators (11) that the hyporeactivity is attributable to the development of bacterial toxins.

Direct observations of peripheral blood vessels during different types of experimentally induced shock have been made recently in a number of different tissues of the rat, rabbit, cat, and dog (10, 12, 18). Although all agree that a marked reduction in peripheral blood flow is the outstanding characteristic of shock, the placing of emphasis on the reaction of the larger blood vessels (12) has stressed a vasoconstrictor tendency, while emphasis on the smaller vessels (18) has stressed a dilator tendency. The present study demonstrates that both sets of reactions contribute to the circulatory collapse and that only in extreme cases does one or the other predominate. The experiments of Page and Abell (12) stressing vasoconstriction represent only one aspect of the syndrome. They have reported an intense vasoconstriction and ischemia in the mesentery of animals subjected to burns or venous tourniquets. It is to be noted that in all their experiments the trauma was applied to all 4 limbs, a condition which in the present study was found to accentuate the effects of fluid loss. In the experiments now reported, fatal results were obtained by a variety of venous tourniquet procedures in which there occurred a wide range of combinations of hypervascular and hypovascular reactions, similar to those with complete tourniquets.

Page (11) obtained evidence for a humoral vasoconstrictor by perfusion of blood samples from animals in shock through isolated rabbit ear preparations and suggests that the subsequent relaxation of the larger blood vessels may be attributed to tachyphylaxis to vasoconstrictors. This theory does not take into account the fact that the development of a hyporeactive condition appears to be dependent upon the presence of a markedly reduced peripheral blood flow rather than upon long continued vasoconstriction. In hemorrhage, hyporeactivity appeared only in those cases in which peripheral blood flow was drastically reduced irrespective of whether vasoconstriction was of long or of short duration. In tourniquet shock, hyporeactivity frequently develops despite the almost complete absence of vasoconstriction and of vasoexcitor substances in the blood. A significant finding, not explained by tachyphylaxis, is the consistent appearance in considerable amount of a humoral hyporeactive or vasodepressor principle demonstrated in test rats as the visceral circulation of the shocked animal becomes hyporeactive.

The taping experiments throw light on the extent to which hyporeactivity in tourniquet

shock can be independent of fluid loss. Taping effectively reduces the peripheral vasoconstriction and hyperreactivity ascribable to fluid loss into the damaged limbs. Despite the curtailment of fluid loss, death occurred with hyporeactive vascular changes. Although it was almost impossible to eliminate fluid loss completely, taping demonstrated that hyporeactivity could develop in certain cases virtually independent of fluid loss.

Perhaps the most important outcome of the present study is the demonstration that a wide range of variability is an integral feature of the shock syndrome.

A broad, over-all picture becomes apparent when the syndrome is analyzed on the basis of relative intensity of compensatory, as against decompensatory, reactions. Both types of reactions were present to some degree in all our animals. Even with a fixed experimental procedure, the relative rôles played by these reactions varied from animal to animal and in some cases even went to the extreme where one or the other factor became almost unappreciable.

Some of the animals went into fatal circulatory collapse with compensatory reactions, such as vasoconstriction, increased frequency of intermittent caliber changes of terminal arterioles and hyperresponsiveness to epinephrine persisting until shortly before death. In these cases the compensatory mechanisms remained intact, but the resulting ischemia progressed to a point where peripheral blood flow was severely curtailed. In other animals compensatory vasoconstriction and hyperreactivity were pronounced but not sufficient to disrupt peripheral blood flow. Hyporeactivity of the terminal vessels and suspension of vasoconstriction developed only after a prolonged period of hypotension, usually appearing about an hour before death. In these cases, hyporeactivity appeared to be related to changes resulting from a prolonged period of poor circulation through the traumatized limbs. The presence of a reduced blood flow through the omentum or mesentery during this protracted period probably predisposes the tissues to hyporeactive vascular changes.

In some animals the compensatory changes were moderate in character and did not appreciably curtail peripheral blood flow. Circulatory collapse occurred following the development of hyporeactivity, with progressive suspension of intermittent arteriolar caliber changes and ultimate unresponsiveness to epinephrine.

In still others almost no compensatory vascular changes were noted. In these hyporeactivity was the factor to which the circulatory failure could be primarily attributed. Hyporeactivity developed early and was followed by a progressive deterioration of peripheral blood flow. Stagnation and pooling, especially in terminal venous vessels, were pronounced.

In addition to variations in response of individual animals, as described, consideration must be given to differences which are introduced by changes in the experimental procedure. Fatal shock could be produced by any of a variety of tourniquet procedures involving 1, 2, or 4 limbs for periods of 4 to 12 hours. In general, the compensatory changes accompanying fluid loss were accentuated with the increase in the mass of tissue subjected to tourniquet occlusion, while decompensatory changes were accentuated by prolonging the period of tourniquet occlusion.

In taking a broad, over-all view of the syndrome, all of these variations must be taken into account. Experimental procedures primarily concerned with obtaining a single reproducible type of shock for statistical analysis are deficient in that they tend to deal with only one aspect of the syndrome. In the present study stress is placed on hyporeactivity because of the tendency in the literature to overemphasize the fluid loss and attending vasoconstrictor aspects of the shock syndrome to almost complete exclusion of other factors.

The significance of the circulatory changes in the omentum and mesentery with respect to vascular changes in other visceral organs was brought out in the autopsy findings. Macroscopically, at autopsy, either an ischemic and pale condition or a congested and bloody appearance was found in the gut, liver, spleen, kidneys, and adrenals, depending upon the corresponding tendency detected during the syndrome in the terminal blood vessels of the omentum and mesentery. The omentum and mesentery usually showed a tendency toward

congestion and stasis to a much lesser degree than was observed in the gut, liver, and kidney at autopsy. Thus, although the vascular changes in the omentum and mesentery do not by themselves materially contribute to the circulatory collapse, they serve as an indication of the general direction of the changes occurring in other visceral structures.

As has been pointed out in a previous paper on "irreversible" hemorrhage shock (18), the development of hyporeactivity created a new problem with respect to therapy. Failure to respond to transfusion appears to be directly related to the development of hyporeactivity. The persistence of this hyporeactivity beyond a certain period of time renders fluid replacement therapy completely ineffective.

SUMMARY

Experiments were performed on dogs, cats, and rabbits in which shock was produced under pentobarbital anesthesia by several different tourniquet procedures. The studies involved two methods. One consisted of continuous observations on specific physiologic reactions of the arteries, arterioles, precapillary sphincters, capillaries, collecting venules, and veins of the exteriorized omentum or mesentery. The other consisted of testing blood samples removed at intervals during the shock syndrome. The serum was injected intravenously into normal rats, and the effect on the arterioles and capillary vessels was noted in the exteriorized mesoappendix.

Tourniquets on 1 limb (cats and rabbits) and 2 limbs (dogs) for periods of 5 to 12 hours generally resulted in fatal circulatory collapse (20 out of 28 animals died). Three types of vascular response were obtained. Hyperreactive responses (compensatory) were accentuated when the tourniquet duration was less than 6 hours, while hyporeactive responses (decompensatory) were accentuated when the tourniquet duration ranged from 7 to 12 hours. In some cases hyperreactive and hyporeactive patterns of response were equally prominent, the syndrome being characterized by an initial hyperreactive state followed by a hyporeactive state in which intermittent arteriolar caliber changes disappeared, the capillaries became filled with increasing amounts of blood, the epinephrine response became subnormal, and there occurred a partial relaxation first of the terminal arterioles and precapillary sphincters and later of the arteries and veins. In others, the hyperreactive stage persisted throughout the greater part of the syndrome, hyporeactivity developing only during the last 20 to 30 minutes. In still others, the hyperreactivity was relatively brief and was followed by a prolonged hyporeactive state.

Four limb venous occlusion for 3.5 hours produced fatal shock with an exaggerated hyperreactive pattern of response, showing intense vasoconstriction and peripheral ischemia until 20 to 30 minutes before death. Fatal collapse with 2 limb venous occlusion for 4 hours showed a similar but milder response. One limb venous occlusion for 4.5 to 6 hours produced fatal shock in 3 of 4 cases. The hyporeactive state became more pronounced, the longer the period of venous occlusion.

Of the 7 dogs whose 2 hind legs were taped and then subjected to 6 to 7 hours of complete tourniquet application, 4 went into fatal circulatory collapse. The nonfatal cases differed from the untaped controls in that the hyperreactivity to epinephrine was only slight and transient, and little or no stimulation of vasomotion appeared. In the fatal cases hyporeactivity developed despite the curtailment of vasoconstriction and hyperreactivity.

Blood samples were taken at intervals during the shock syndrome and the serum injected into test rats. The humoral activity of the samples was determined by the reaction produced in the small blood vessels of the mesoappendix of the test rat. Control blood samples taken prior to tourniquet application had no effect on the reactivity of the rat vessels. Blood taken during the period in which the visceral circulation in the dog showed a hyperreactive pattern gave, in the rat test, a vasoexcitor response. Blood taken during the intermediate period in which the hypernormal epinephrine responsiveness was falling and vasomotion was subnormal or absent gave, as a rule, in the rat test, no demonstrable response. Blood taken during the period in which the visceral circulation in the dog showed a hyporeactive pattern produced, in the test rat, a vasodepressor response.

CONCLUSION

The initiating factor in the peripheral circulation is a reduction in rate and amount of blood flow. This occurs while the damaged limb is swelling and is associated with vasoconstriction and with hyperreactivity of the terminal vessels as observed in the mesentery and omentum.

When the syndrome is fatal two sets of contributory factors are detected: an increased viscosity of the blood, indicated by a rise in hematocrit, and the development of hyporeactivity of the terminal blood vessels. The hyporeactivity occurred while the peripheral flow was still good and resulted in pooling of blood in the capillaries and venules, thereby intensifying the reduction in the circulating blood volume. In many cases, hyporeactivity was the decisive factor in the syndrome.

Circulatory collapse in tourniquet shock is due to a reduction in blood volume caused by: (a) loss of fluid into injured limbs and (b) sequestration of blood from the active circulation by pooling in the capillary bed and collecting venules. The latter is due to the development of a hyporeactive factor, which progressively interferes with the peripheral vascular compensatory mechanisms.

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EFFECTS OF THE PARENTERAL ADMINISTRATION OF FLUIDS ON THE METABOLISM OF ELECTROLYTES DURING POSTOPERATIVE CONVALESCENCE

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THE therapeutic value of the intravenous administration of fluids during the course of any illness in which it has been difficult to maintain adequate fluid intake by mouth or in which the loss of fluid has been excessive is well established. However, the administration of large amounts of fluid directly into the blood stream may occasionally produce unforeseen and inexplicable complications. Varying degrees of edema after repeated administration of fluids intravenously may be rationally explained as a complication of the sodium chloride and water which have been administered. After this obvious reason for edema has been evaluated, such causes as malnutrition, loss of protein by drainage or hemorrhage, sepsis and impaired renal function may be given the etiologic credit they deserve.

Our interest concerning the intravenous administration of fluids pertains to certain practical aspects of therapy. Most of the literature on this subject suggests that a middle-of-the-road course be pursued when fluids are to be administered parenterally. For example, one should administer a liter of physiologic saline solution and a liter of a 5 or 10 per cent solution of dextrose in distilled water, or equal parts of these solutions. A patient who receives 3,000 cubic centimeters of a solution containing 0.45 per cent of sodium chloride solution or 1,500 cubic centimeters of physiologic saline solution during 24 hours receives 12.75 grams of sodium chloride which is 4 or 5 grams more sodium chloride than is ingested in the normal diet. A physiologic solution of sodium chloride, however, is the favorite solution for intravenous administration in spite of warnings concerning its injudicious employment. Coller, Dick and Maddock have shown that retention of water is a frequent occurrence after the administration of solutions of sodium chloride to patients who are very ill after surgical operation. However, the parenteral use of isotonic solutions of sodium chloride possibly has become a habit because this solution may be a means of saving the lives of many patients who have an intestinal obstruction both before and after surgical treatment. Also there is abroad the general idea that intravenous administration of fluid produces a greater diuresis than does oral administration of the same amount of fluid. Of course the varying conceptions of the diuretic effects of oral versus parenteral administration of fluid is unimportant. No one would administer fluid intravenously in a case in which an adequate amount of fluid could be administered by mouth. Fantus has appropriately suggested that the intravenous administration of fluid produces less diuresis than does oral ingestion. Matas has emphasized what he considered the dangers of the administration of isotonic solutions of sodium chloride. It may be said therefore that the parenteral administration of isotonic solutions of sodium chloride is universal and that the procedure is not often complicated by any very grave untoward effects. The object of the present study was to determine, if possible, what changes occur in the excretion of the fixed bases and chlorides during the prolonged intravenous administration of isotonic solutions of sodium chloride (1 per cent) and solutions of dextrose (5 or 10 per cent) or mixtures of these solutions.

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MATERIAL AND METHOD

The cases selected for study were those in which under ordinary circumstances large amounts of fluid would be administered intra-

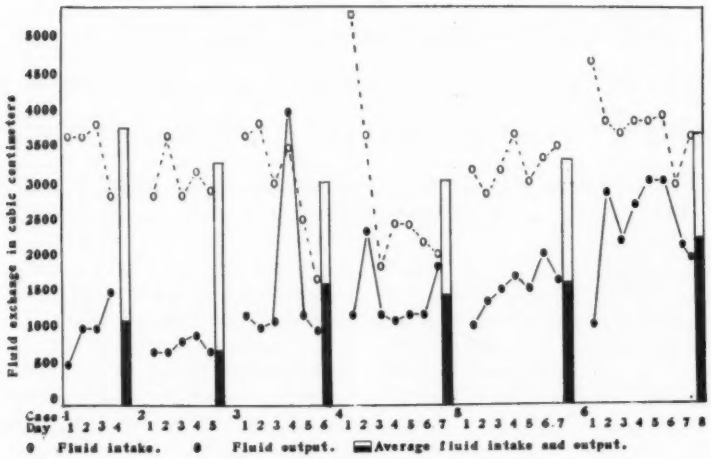
Fluid exchange in cubic centimeters
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Case 1 2 3 4 5 6
Day 1 2 3 4 1 2 3 4 5 1 2 3 4 5 6 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 8
Fluid intake. Fluid output. Average fluid intake and output.

Fig. 1. Daily intake and output of fluid.

venously. They were all cases of carcinoma of the colon; in all of the cases the involved segment of the colon had been resected. The usual postoperative treatment was not altered in any manner. Blood was collected within an hour after the operation and again at the conclusion of the study. The urine was collected and the total amount obtained in each 24 hours of the period of observation was examined. In Case 4, an indwelling catheter permitted the accurate collection of the specimens of urine. In the other cases the patients were often unable to micturate at the end of each day. However, the total collections of urine during the periods of study were reasonably accurate. Vomitus and duodenal drainage were also collected. The one patient who passed feces during the period of study was given a tablespoonful of powdered charcoal at the end of the final period of 24 hours and all feces passed prior to the appearance of the charcoal were collected in one container. The results of the analysis of this specimen were included in the output for the last day (Case 3, 6th day). Samples of the solutions of sodium chloride that were injected were analyzed and the composition was found to be almost uniform. The average composition of the analyzed samples served as a basis for computing the intake of sodium and chloride. The Ringer solutions administered in Case 5 were individually analyzed. Aliquot samples of the various fluids which were given orally were mixed and analyzed. During the entire period of study the patient in Case 1 received only a 5 per cent solution of dextrose. If the dextrose that was administered parenterally was utilized, 1,770 calories were thus administered in Case 1. Similarly the patient in Case 2 received 1,220 calories in 5 days; the patient in Case 3 received 1,796 calories in 6 days; the patient in Case 4 received 3,207 calories in 7 days; and the patients in Cases 5 and 6 received 3,485 and 4,777 calories, respectively, in 8 days.

Samples of blood for the analyses were collected under oil in tubes containing heparin. The following analytical methods were employed: for plasma sodium, the method of Butler and Tuthill; for plasma potassium, Hartzler's modification of the method of Shohl and Bennett; for chlorides in plasma, the method of Keys; for calcium in plasma, the method of Tisdall and Kramer; for magnesium in plasma, the method of Denis. The amount of base contained in foods, feces, and urine was determined on ashed samples by means of the same procedures as used for the determination of the amount of sodium, potassium, and magnesium in the blood plasma. The calcium was precipitated as the oxalate by a modification of the method of Washburn and Shear. The amount of chloride in the urine

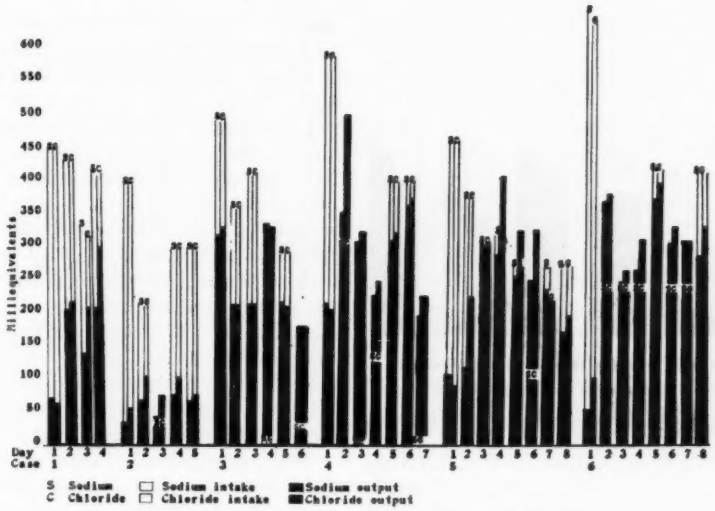

Fig. 2. Daily intake and output of sodium and chloride.

was determined by the open Carius method, by means of reagents suggested by Peters and Van Slyke.

RESULTS

The greater part of the fluid intake was given parenterally, but, toward the end of the period that each patient was being studied, small amounts of water were taken by mouth as "sips." Occasionally, the "sips" consisted of fruit juices. When the fluid was fruit juice or other liquid food, an aliquot was taken for analysis and the volume was included in the total intake. Figure 1 is a graphic representation of the daily intake and output of fluid. At the end of the period of study in each case is given an average of the daily intake and output of fluid. When a transfusion was given, the total volume of blood was included in the fluid intake and the total amount of sodium, potassium, magnesium, calcium, and chloride of the blood was added to the total intake of these substances. In one case (Case 5) the patient received Ringer's solution in the last 2 days of observation and the amount of base and chloride of this solution was likewise included in the results of the analysis of the intake. As is indicated in the graph, the fluid output exceeded the intake only once and that was in Case 3 on the 4th day of the study. The volume of the total fluid output is the sum total of the fluid lost in the urine, by duodenal suction, and, on one or two occasions, in vomitus. The total output of sodium, potassium, magnesium, calcium, and chloride includes the amount of these substances lost in the vomitus, duodenal fluid, and urine. The amount of fluid and electrolytes lost through sweating and respiration could not be accounted for in this study. The experimental work was done in cool weather. The losses of electrolytes through the sweat probably were not of very great importance.

The daily intake and output of sodium and chloride is shown in Figure 2. In Figure 3 the averages of the daily excretion of sodium and chloride are shown. Only in Case 4 did the average excretion of these substances exceed the average intake. Each individual displayed marked differences in the exchange of sodium. In Cases 1 and 2 (Fig. 2) the patients excreted a very small percentage of the total intake of sodium. At the end of the period of observation we were unable to account for 1,244 milliequivalents of sodium in Case 1 and 952 milliequivalents of sodium in Case 2. In Case 3 the patient apparently retained 636 milliequivalents of sodium during the first 3 days. However, during the 4th day, 3,440 cubic

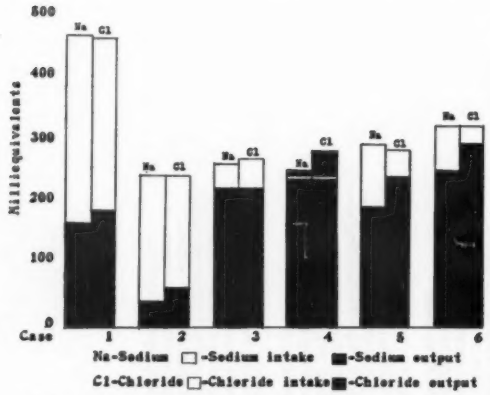

Fig. 3. Average daily excretion of sodium and chloride.

centimeters of a 5 per cent solution of dextrose were given intravenously, 165 cubic centimeters of water were administered orally, and 4,050 cubic centimeters of urine were excreted. This large volume of urine contained a half of the 636 milliequivalents of sodium which had been retained or were not accounted for. At the end of the 6-day period of observation, however, there were still 246 milliequivalents of sodium which were unaccounted for and thus probably retained. In Case 4 the excretion of sodium exceeded the ingestion of sodium by 38 milliequivalents during the 7 day period of study. The intake of sodium in this case was 39 milliequivalents, which is 260 milliequivalents less than the average daily intake of 299 milliequivalents in all the cases studied. In Case 5 the patient excreted only 1,517 of the total 2,338 milliequivalents received, which leaves 821 milliequivalents unaccounted for or retained. In Case 6 the patient maintained an output of fluid which was consistently higher than that excreted by any of the other patients, yet 483 milliequivalents of sodium were unaccounted for or retained at the end of the 8 day period of study.

Generally, the intake of chloride was the same as the intake of sodium since the chloride salt of the sodium was administered parenterally. The excretion of chloride (Fig. 2) was not the same as the excretion of sodium except approximately in Case 3 (Fig. 2). In all of the other cases more chloride than sodium was excreted. The greatest loss of chloride was observed in Cases 5 and 6 and this loss or output probably can be accounted for by the fact that in these 2 cases large volumes of fluids were removed by means of duodenal suction.

The intake of magnesium and calcium was mostly that included in the liquids administered by mouth and transfusion. The daily intake of magnesium for all patients varied from none at all to 2.9 milliequivalents. The daily excretion varied from 1.4 to 15.3 milliequivalents. The intake of calcium varied from none at all to 5.5 milliequivalents and the excretion varied from 0.6 to 13.9 milliequivalents. The excretion of calcium approximately paralleled the excretion of magnesium.

The intake of potassium was mainly that received by blood transfusion.

The excretion of potassium seemed to be definitely increased during the first 4 postoperative days. This increased excretion of potassium is probably the same phenomenon observed by Gamble, Ross, and Tisdall and Benedict during fasting. They observed that in the early days of a fast the excretion of potassium was from two to three times greater than during equal periods later in the fast. Gamble, Ross and Tisdall expressed the opinion that increased excretion of potassium was related to a reduction in the stored glycogen and consequent loss of the intracellular water in which it had been dissolved. Silvette, Britton, and Kline agreed with Gamble, Ross and Tisdall, concerning this increased excretion of potassium. Byrom found that the increased initial loss of potassium occurred if ample supply of carbohydrate was administered but could be prevented if both potassium and carbohydrate were given. A most important, but not a new, conception of the loss of potassium was advanced by Thaler, who observed that the excretion of potassium was increased if the intake of sodium chloride was increased. Sodium and potassium are closely related chemical bases and deranged concentrations in physiologic fluids or in fluids administered are liable to be accompanied by deranged excretions.

The intake of nitrogen was not determined. The nitrogen, like potassium, was mainly included in the blood transfusion. The daily excretion of nitrogen varied from 2,370 to

15,765 milligrams. The excretion of nitrogen tended to be low during the first postoperative day and higher than the average during the 3 succeeding days.

Generally the concentrations of sodium, potassium, calcium, magnesium, chloride, hemoglobin, and the hematocrit reading showed no great change.

In spite of the large intake of sodium and chloride (the intake of sodium averaged 299 milliequivalents per day in all cases), the concentration of the sodium and chloride in the plasma remained approximately constant or was reduced in all cases. It is of interest here to recall that considerable amounts of sodium were retained or unaccounted for in all cases except Case 4. The total concentration of base in the plasma paralleled that of the sodium and was generally slightly reduced. Reduction in the concentration of the hemoglobin and a decrease in the normal hematocrit reading were the rule and probably indicated that the blood had been diluted.

COMMENT

The patients observed in this study differ in several respects from one who is being starved. They all had had an anesthetic and an abdominal operation, and fluids containing sodium chloride and solutions of dextrose were administered. However, little nourishment was taken by mouth. In the first few days of starvation, according to Gamble and his co-worker, destruction of protoplasm, with its attendant loss in body weight, is accompanied by losses of intracellular and extracellular bases, chiefly potassium and sodium, and body water from the intracellular and extracellular compartments in such amounts that the base content of the plasma and extracellular fluids bathing the cells remains essentially unchanged. Our Case 4 was the only one in which we observed a negative sodium balance comparable to that seen in starvation. In the other 5 cases the patients apparently retained much of the administered sodium, and the concentration of sodium in the urine was relatively low rather than high. At the same time, the average volume of urine excreted during the 24 hour period by our patients was less than the optimal normal excretion of 1500 cubic centimeters. It seems evident, therefore, that the retained sodium in these cases was accompanied by an appropriately equivalent retention of water, a finding which is in harmony with the interpretation of numerous studies on the relationship between base and water metabolism. Much of the water injected was consequently not available for replacement of fluid lost by evaporation, perspiration, or in the urine, which together should amount to about 3,500 cubic centimeters in adults, according to the standards proposed by Coller, Dick, and Maddock.

That the foregoing conditions may not be optimal for the performance of normal physiologic functions by the kidneys is illustrated by the data obtained in Case 5. During the 8 day period of study, 2,338 milliequivalents of sodium were administered. Fifteen hundred and seventeen milliequivalents, or not quite two-thirds of the sodium, were excreted. The concentration of sodium in the urine increased until it reached 161 milliequivalents per liter on the 6th day. The concentration of sodium in the urine then diminished rapidly to 62 milliequivalents per liter on the 8th day. The specific gravity of the urine decreased from 1.023 to 1.008. We have observed that oliguria and practically an anuria can be produced by the administration of sodium chloride in cases in which renal function is decreased. The data in this study seem to indicate that the functional activity of the apparently normal kidney at times may be reduced greatly by the administration of sodium chloride. The impression that normal kidneys can be depended upon to retain what the body needs and excrete the excess is so nearly true that this belief may be dangerous. The elasticity of normal renal function is enormous. It should, however, be kept in mind that once any organ is overloaded fatigue may come on rapidly and prove disastrous.

The parenteral administration of physiologic saline solutions during intestinal obstruction in cases in which chloride has been lost produces such immediate benefits that one feels that physiologic solutions of sodium chloride are always safe to administer in large quantities. Nothing is farther from the truth. Certain fundamental facts must be kept in mind

and no formula can be given to guide those who wish to ignore these facts. The average diet contains approximately 2 grams of sodium (equivalent to about 5 grams of sodium chloride), although one may take as much as 10 or more grams of sodium chloride daily. It is interesting to compare an intake of 10 grams of sodium chloride with the amount received by a patient who is given 3,000 cubic centimeters of physiologic saline solution intravenously. The patient receives about five times the average daily intake of sodium chloride required for the healthy adult and two and one-half times as much as the individual who through habit has taken 10 grams daily. It is by ignoring these simple facts that patients who have not lost chlorides by vomiting, by duodenal drainage, or by extensive burns of the surface of the body often leave the hospital, after surgical operations, with a small amount of dependent edema, "probably nutritional in origin."

SUMMARY

During postoperative parenteral administration of solutions of sodium chloride to patients who were not taking food, considerable retention of sodium occurred in 5 of 6 cases. The concentration of base in the plasma did not change appreciably. The volumes of urine were less than optimum, and 1 patient became unable to excrete concentrated urine, possibly as the result of the administration of too much sodium chloride. Under these conditions water must be retained with base, and we wish to emphasize that water administered in the form of physiologic saline solution is not available for the important requirements of evaporation and perspiration.

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THE TREATMENT OF THROMBOPHLEBITIS

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THE disabling and sometimes disastrous consequences of venous thrombosis are well known to every physician. The etiology and resultant pathology of this condition have been subjects of varied opinions since John Hunter first described thrombosis as a sequel of phlebitis. The treatment has not changed much, however, as it has been little except symptomatic. During the past few years anticoagulant therapy has gained prominence in the treatment of thrombophlebitis and its associated complications.

The first of these substances used was heparin after its purification by Murray and Best. This substance, however, has certain inherent difficulties in regard to its use: it is expensive, must be given intravenously; frequent determination of coagulation must be done; its results are not predictable, and its margin of safety appears to be narrow.

With the discovery of dicumarol[1] by Link (3) and his associates in 1940, an anticoagulant, not presenting most of these difficulties, was made available for the treatment of thrombotic phenomena.

Some investigators have tried dicumarol in the treatment of thrombophlebitis and have reported favorable results. On the other hand, there has been some adverse comment about the use of anticoagulants in the treatment of thrombophlebitis. The main criticism according to DeBakey has been that the series of investigations are not adequate, nor are the results sufficiently impressive to justify definite statements.

In an effort further to evaluate the use of dicumarol we have subjected all patients with thrombophlebitis to a uniform type of therapy.

This series consists of 67 cases of thrombophlebitis and its complications. We have arbitrarily divided the cases into four groups on an anatomical basis. These consist of (1) superficial phlebitis, (2) deep phlebitis, (3) superficial and deep, (4) pulmonary embolization with or without a demonstrable phlebitic site.

The treatment and results for each group are discussed separately. Prothrombin times were done daily. The technique using the method of Shapiro, with modifications, is indicated below.

TECHNIQUE

1. Remove lung from freshly killed rabbit.
2. To remove blood, wash lung for about 15 minutes in cold running water. Blot out excess with filter paper.
3. Cut in small pieces; place in evaporating dish.
4. Place dishes in desiccator. (Drying agent barium dioxide). Attach to suction apparatus to form a vacuum for about 10 to 15 minutes.
5. Place desiccator in incubator at 37 degrees for 24 hours. (Drying process).
6. Remove pieces of lung from desiccator, grind finely in mortar.
7. Keep in refrigerator. (Good about 4 weeks.)

THROMBOPLASTIN

1. To 100 milligrams of rabbits' lungs (thromboplastin)
2. Add 5 cubic centimeters of normal physiological saline (0.85).
3. Inactivate thromboplastin for 10 minutes in water bath at 57 degrees C. Stir constantly.
4. Remove from water bath and stir until thromboplastin reaches room temperature.
5. Add 5 cubic centimeters of calcium chloride (1.11 gr. to 500 c.c.). Shake thoroughly.
6. Centrifuge for 4 minutes at 1800 revolutions. Use supernatant fluid.

OBTAINING BLOOD SPECIMEN

Using 20 gauge needles, take 4.5 cubic centimeters of blood to 0.5 cubic centimeters of sodium oxalate (1.34 to 100 c.c.). Centrifuge, remove plasma.

PROTHROMBIN DETERMINATION

1. Place plasma in water bath kept at a constant 38 degrees' temperature.
2. In small tubes add 0.2 cubic centimeter of thromboplastin.
3. To thromboplastin add 0.1 cubic centimeter of whole plasma. Start stop watch immediately. Use

This work was done under a research grant from the Wm. G. Keufel Fund, Lenox Hill Hospital.
Technical assistance and procedure by Miss Ruth Lipkin, A.B.
[1]Dicumarol furnished by Dr. G. R. Hazel of Abbott Laboratories.

a wire loop to pick up complete clot when it is formed. Record time of result.

SUPERFICIAL PHLEBITIS

In this group there are 11 cases; 8 female and 3 male. The ages varied from 25 to 61 years; 4 were postpartum, 2 antepartum, and 5 were cases of phlebitis of long standing, unassociated with any known etiological factor. All of these patients were treated in the same fashion. Dicumarol was administered in sufficient dosage to keep the prothrombin time prolonged to double the normal value of that particular patient.

Wet boric acid dressings were applied continuously to the affected area and ½ grain papaverine was given at irregular intervals for excessive pain. The average number of days in bed was 10, and the criteria taken for remission of the attack were diminution or disappearance of pain or tenderness over the affected areas, as well as normal temperature and pulse. Dicumarol was discontinued when these conditions were fulfilled, and the patient was then allowed out of bed and active motion, usually with the application of an Ace bandage, encouraged. The average total dose of drug was 1000 milligrams.

These patients have been followed for an average of from 6 to 10 months with no further recurrences reported to date. It is interesting to note that Case 7 had had repeated attacks of phlebitis during the past 10 years, each lasting from 3 to 4 months. This patient was out of bed and feeling well in 9 days and has had no further symptoms. Two interesting cases, especially from the standpoint of the obstetrician, Cases 1 and 10 in this group, were 2 antepartum patients who developed severe superficial phlebitis during the 7th and 3d months of pregnancy, respectively. Patient 1 had marked tenderness and redness along the course of almost all the superficial veins of the thigh. No primary site of infection could be found. The patient was immediately started on the aforementioned regimen. On the 4th day when the patient was in the therapeutic range she was entirely free of pain for the first time. By the 10th day she was completely asymptomatic, and then was allowed out of bed. She was followed throughout the rest of her pregnancy and did not develop recurrence of phlebitis. Two months later she delivered a normal male child. There was no excessive bleeding at the time of delivery and the baby showed no untoward effects due to dicumarol. The patient was followed during her postpartum course but showed no signs of phlebitis. The other patient also showed good response but had not reached term at the time of this report.

Although this series of cases is small, they are representative of the type of superficial phlebitis usually observed. The rapidity of response to therapy and the long remissions encourages one to continue further therapy along these lines. It is further interesting to note that in none of these cases was there an attempt to control infection *per se* with either chemotherapy or other antiseptic agents.

DEEP PHLEBITIS

This group contains 27 patients. Nineteen of these were females, 8 males. The ages varied from 18 to 67 years. Four of these patients were postpartum, 16 were postoperative, and the 7 remaining without any etiological factor. All of these patients were treated in the same way. Dicumarol was begun as soon as the diagnosis was made. The involved extremity was elevated, a cradle placed over the limb, and an ice bag applied to the point of maximum tenderness. The method of administering dicumarol was the same as described and prothrombin times were done daily. The largest dose administered was 2300 milligrams. The smallest was 500 milligrams. The criteria for remission were normal temperature and pulse, lack of tenderness over the affected veins as well as loss of pain and marked decrease in the amount of swelling. When these criteria were fulfilled, the patient was allowed out of bed and an elastic stocking or an Ace bandage was applied. The prothrombin time was kept within the therapeutic range for at least 24 hours after patient got out of bed.

Under this regimen the average time in bed was 10.5 days with a range of 5 to 23 days. Pain usually subsided within 24 hours after the patient's prothrombin time was in the therapeutic range. Little if any sedation was needed during the rest of the course. Most

significant is the fact that there were no episodes of pulmonary embolization. The thrombotic process appeared to remain localized. No untoward effects from dicumarol occurred. In Case 13, the prothrombin time went as high as 70 seconds but there was no evidence of hemorrhagic phenomena.

SUPERFICIAL AND DEEP PHLEBITIS

There are 9 patients included in this group, 7 of which were female, and 2 male. The age distribution was from 30 to 72 years. Five cases were postoperative hysterectomies, 1 was an antepartum patient in her 8th month, and 3 were phlebites without any known etiological factor. The regimen followed in these cases was the administration of dicumarol as here outlined above, elevation of the leg, wet boric acid dressings to the affected area, and papavarine in doses of ½ grain every 4 hours, for pain. The largest total dose administered in these cases was 1400 milligrams and the smallest 600 milligrams.

These patients remained in bed for an average of 14.7 days with a range of 7 to 25 days. There were no complications referable to embolic phenomena nor were there any toxic effects due to dicumarol. Patient 1 was a primipara who developed redness and a slight swelling over the medial aspect of the lower extremity just below the knee. There was marked tenderness over the short saphenous vein. The regimen outlined was initiated and the symptoms subsided within 7 days. This patient was delivered of a normal male child 2 months later. There were no concomitant hemorrhagic phenomena.

The second interesting case, Case 2, was a patient 72 years old. He had had a chronic phlebitis for the past 10 years. There was definite evidence of superficial and deep phlebitis. The regimen outlined was instituted and the patient was kept under therapy for 15 days. There was apparent subsidence of phlebitic symptoms and therapy was discontinued. The follow-up course showed persistent edema. Three weeks later this patient suddenly went into coma and died despite supportive therapy. An autopsy showed fresh thrombosis throughout the iliac veins involving the vena cava.

Patient 7 was admitted in 1936 for a salpingo-oophorectomy. Eight days following the operation she developed deep phlebitis of the lower extremity and 10 days later a pulmonary embolus. She remained in the hospital for 3 months on symptomatic therapy. She was readmitted in 1939 with swelling of the leg as well as pain in chest, cough and blood tinged sputum. The diagnosis at this time was recurrent phlebitis with pulmonary embolism. From 1939 to 1943 this patient was seen on numerous occasions in the clinic, complaining of pain and swelling in one lower extremity. She had had various forms of therapy including application of leeches, cold compresses, elevation of the part, with little result. In 1943 she was admitted to the hospital for repair of ventral hernia. This time she had a slight swelling of the left lower extremity, with tenderness and redness along the medial aspect. The usual regimen was begun. Patient was kept on dicumarol for 16 days. This time the prothrombin time was allowed to return to normal and the ventral hernia repaired. On the 3d postoperative day dicumarol was again begun, and she was kept in therapeutic range for the next 10 days. She was discharged with no symptoms of active phlebitis.

PULMONARY EMBOLIZATION

This group includes 10 patients, 7 of which were female and 3 male. Age distribution varied from 28 to 65 years. There was no previous history and there were no symptoms of phlebitis in any of these cases, the first symptoms being those referable to embolus of the lung. Eight of the patients had one pulmonary embolus, while 3 had two episodes. These patients fit into the group described by Homans as silent thrombophlebitis in which the first symptom is referable to the embolus and not to the original phlebitic site. In 8 of the patients the conditions were postoperative, each patient having had some type of pelvic operation. The most obscure case was that of a 65 year old woman who had a typical episode of pulmonary infarction of unknown etiology.

All patients were treated in the same fashion. Dicumarol was begun as soon as the pa-

tient was seen and continued in sufficient doses to keep the prothrombin time elevated to twice its normal value. The only other therapy was an adequate amount of sedation to control pain.

While under therapy none of these patients had any further episodes of pulmonary emboli. This held true even for those who had more than one previous episode. These patients remained in bed an average of 14 days, the longest time being 20, the shortest 13. One patient was found to be resistant to the ordinary dose of dicumarol. The prothrombin time in this case was never raised above 25 seconds. When a second group of pulmonary emboli occurred she was treated with heparin.

The results in this group of patients were fairly uniform while under treatment. There were no toxic effects due to dicumarol, and the drug was administered and controlled without difficulty.

SUMMARY

The above presentation, not lending itself to statistical analysis, indicates some interesting points in the therapy of phlebitis.

The diminution in the length of time of treatment, the lack of complications referable to phlebitis as well as to dicumarol, make this form of therapy worthwhile. None of these cases while under treatment or in the posttreatment period, developed emboli. In those cases, having had previous embolic phenomena, there was no further evidence of it after therapy was begun. Further, in none of the 67 patients did other foci of thrombophlebitis occur either in the treatment or posttreatment periods.

Pain, which is an outstanding feature of thrombosis, is markedly decreased in direct relationship to the initial elevation of the prothrombin time; i.e., when the patient is in the therapeutic range the amount of sedation needed is markedly diminished. This very interesting feature was first pointed out by Zucker.

In contrast to other types of anticoagulant therapy, dicumarol appears to have a wider margin of safety. Prothrombin time in these cases varied between 15 and 70 seconds. Despite this marked prolongation of the prothrombin time, there was no evidence of hemorrhagic diatheses.

We must not, however, develop a false sense of security in this wide margin of safety as each individual varies in his response to a given dose of dicumarol. Consequently, prothrombin times must be done daily or at least preceding the administration of any given dose. Reference to the tables of any group of patients presented will indicate that despite the uniformity of the initial doses, subsequent doses varied markedly.

The initial doses consisted of 300 milligrams the first day, and 200 milligrams the second day. Following these doses from 50 to 200 milligrams in 24 hours were given. The guide to the proper dose was the prothrombin time. If after 500 milligrams the prothrombin time had risen to double its initial value no further dose was given. If it was rising rapidly but had not reached the therapeutic range, i.e., double its initial value, no dose was given. If there was no rise, or it was rising slowly, from 50 to 200 milligrams was given, depending upon the initial elevation. This same scheme was followed throughout the course.

Under this regimen there usually was a latency of 24 to 72 hours before the prothrombin time was affected. One must be wary of overdosage during the latter part of the latent phase. The third dose in our cases was almost always 100 milligrams.

Of the patients treated there were 37 treated for postoperative sequelae, 22 were antepartum and postpartum cases, and 17 were phlebitis cases without known etiological association. Dicumarol was begun during various intervals of the postoperative period, but in no case was it necessary to begin treatment before the 3d postoperative day. As far as could be determined there was no interference with wound healing and no hematomas developed. In the obstetrical cases, 19 of which were postpartum, there was no increased vaginal bleeding nor was the postpartum period affected in any way. In these cases dicumarol was begun as early as 24 hours following delivery. Three antepartum patients had normal deliveries, one of these having received dicumarol in the last month of the third trimester.

In these series only one resistant case was encountered and her prothrombin time did not go above 20 seconds despite a total dosage of 2100 milligrams.

We have had little experience with other methods of treating thrombophlebitis, such as paravertebral procaine sympathetic block, or venous section with ligation. This latter procedure was used in one case of deep phlebitis of the femoral vein combined with anticoagulant therapy. However, the lack of complications, due to either the thrombophlebitis or dicumarol would seem now to make anticoagulant therapy alone the procedure of choice.

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THE SURGICAL ANATOMY OF THE FACIAL NERVE

With Special Reference to the Parotid Gland

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ALTHOUGH the incidence of parotid tumor may be as low as 0.06 per cent (Sistrunk, 1921), treatment of the lesion is fraught with such difficulty that any aid, offered by anatomy to the surgeon, would be of value. While injury to the facial nerve is not vitally damaging, the resultant cosmetic deformity brings great psychic distress to the patient. In an attempt to avoid the latter effect, roentgen therapy has often been resorted to in the management of these tumors. Bailey (1941), arguing for total parotidectomy, calls attention to the radioresistance of most of the tumors; he also mentions the great tendency to recurrence because of the technical difficulties involved in the operative procedure. McFarland (1933), in studying over 400 cases, reported a 30 per cent recurrence of parotid tumors locally removed, especially those of smaller size.

Many authors have discussed the surgery and pathology of the parotid area, but relatively little has been written about the exact relation of the gland to the facial nerve. The most extensive anatomic study of the nerve (Tortella, 1935) is based upon only seven specimens. The purpose of the present study, therefore, is to furnish such information on the nerve and parotid gland accumulated from a large series of specimens.

MATERIALS AND METHODS

The series herein reported upon consists of 100 facial halves selected from specimens in the anatomical laboratories of Northwestern University Medical School.[1] The specimens were adult whites and negroes (79 white, 21 negro), mostly male (82 males, 18 females). Only specimens with complete dissection of the facial nerve were included. No attempt was made to study bilateral configurations.

A fixed method of exposure was followed, devised to preserve the relationship of the gland to the nerves. The skin and superficial fascia over the parotid area were carefully removed, from posterior to anterior. The free anterior border of the parotid gland was then mobilized, and a careful search was made for the emerging branches of the facial nerve, particularly the temporal or zygomatic portions. The mandibular and cervical divisions were next uncovered along the anteroinferior border of the gland. These divisions being used as guides, the dissection was then carried into the gland itself. In virtually all instances, a natural cleavage plane was found to exist between the lobes of the gland, which allowed the dissector to locate the main trunk of the nerve at its point of division. Careful individual drawings of the area were then prepared, to show the configuration of the main portions of the nerve and the anastomoses between its adjacent divisions and branches.

In the greater number of the specimens (66) the distance between the point of bifurcation of the nerve and the external angle of the mandible was recorded (Table I). In 75 specimens the height and width of the parotid gland were measured, and the shape recorded. The presence or absence of accessory glands and the general configuration and course of the main parotid duct were also noted.

All of the illustrations were prepared from specimens selected from the series.

OBSERVATIONS AND DISCUSSION

Developmentally, the relationship of the parotid gland to the facial nerve is a secondary one, since the gland migrates backward from its original site of pharyngeal outpouching. Controversy, however, has developed as to the mode of formation of the lobes of the gland. Grégoire (1912),

TABLE I.—HEIGHT OF NERVE ABOVE ANGLE OF JAW

Height cm.	Number	Height cm.	Number
1.4–1.69	1	3.2–3.49	13
1.7–1.99	0	3.5–3.79	6
2.0–2.29	2	3.8–4.09	10
2.3–2.59	5	4.1–4.39	8
2.6–2.89	7	4.4–4.69	5
2.9–3.19	9	Average—3.4 cm.	66

Contribution from Anatomical Laboratory of Northwestern University Medical School.

[1]Approximately 50 additional specimens were examined; although imperfect in respect to some details of nervous branching, their general structure would support all statements made hereinafter.

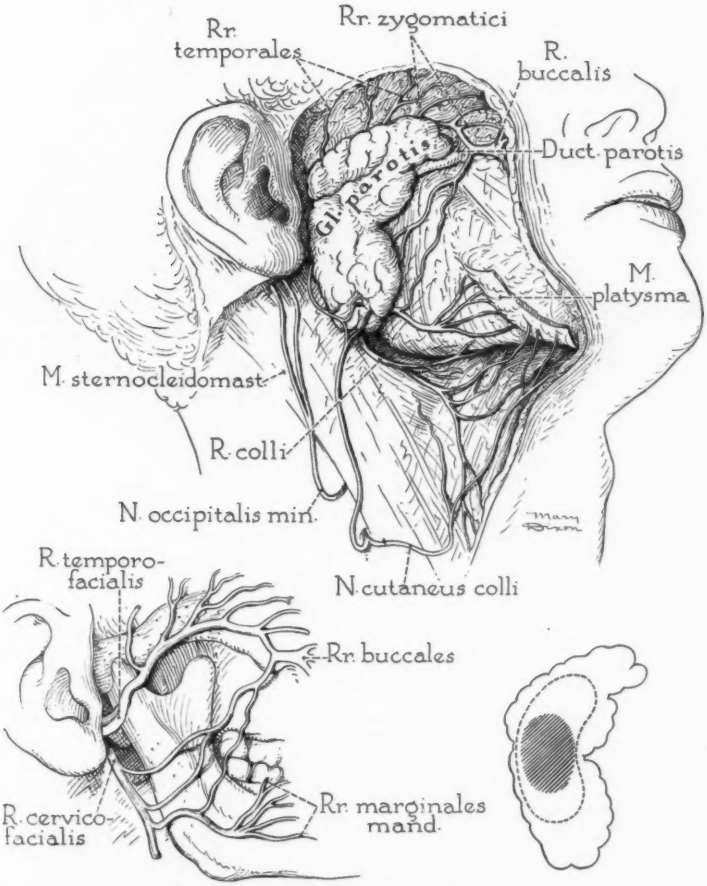

Fig. 1.

Fig. 2.

Fig. 3.

Figs. 1 to 3. Facial nerve and parotid gland; superficial and deep dissections. Adult male, negro. Showing the divisions and rami of the nerve and their relation to the gland, and to the mandible and zygomatic arch. In Figure 3, lower right, the margin of the deep lobe (broken line) and isthmus (cross-hatching) are shown diagrammatically.

from a study of 60 adult and 8 fetal glands, concluded that the deep lobe was formed by a migration of a portion of the superior pole of the gland, the latter retaining connection with the superficial lobe which remained situated above the facial nerve. McWhorter (1917), from an examination of 66 adult parotids and 16 in fetal and newborn specimens, was, on the contrary, of the opinion that the gland was H-shaped, with the connecting arm (or isthmus) between the two diverging portions of the facial nerve. Rouvière and Cordier (1934), after reconstructing two glands, came to the conclusion that both Grégoire and McWhorter were correct; in the 31 millimeter fetus the gland was found to be entirely superficial, while in the 51 millimeter fetus there were projections which passed over the facial nerve superiorly as well as some which passed between the two portions of the nerve to form a deep lobe.

The present authors found that the general relationships which were described by McWhorter were recognized in their specimens. The facial nerve, lying between two lobes of the parotid, partially separates the gland into a large superficial and a small deep portion, the two parts being connected by a slender isthmus which passes between the two diverging portions of the nerve (Fig. 3).

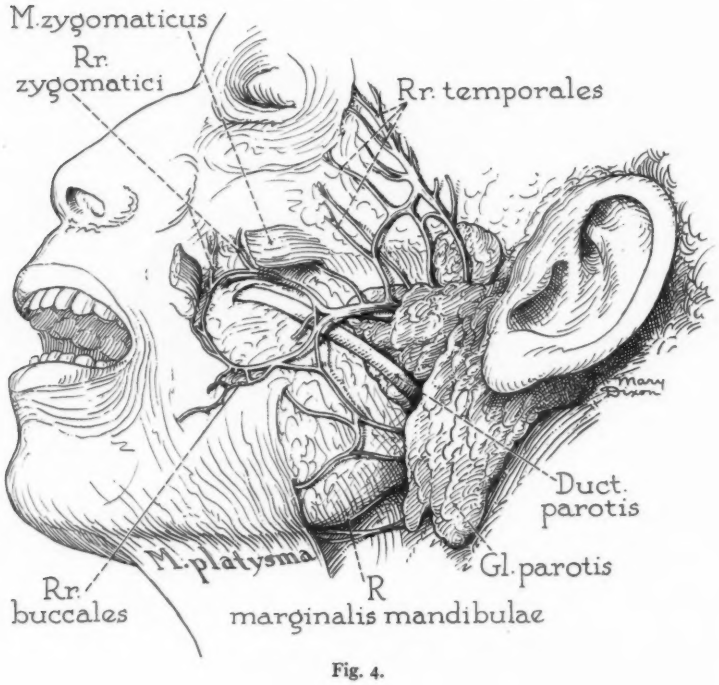

Fig. 4.

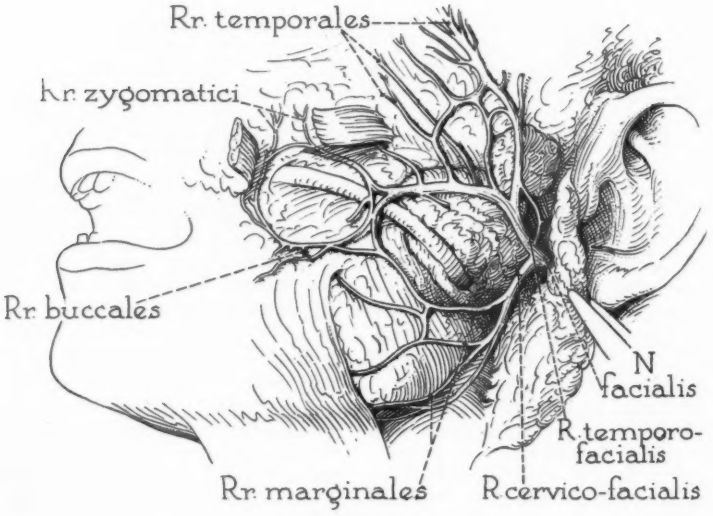

Fig. 5.

Figs. 4 and 5. Facial nerve, superficial and deep dissections. Adult male, negro. Showing secondary anastomosis between the main divisions. The secondary loop surrounded the isthmus (transected).

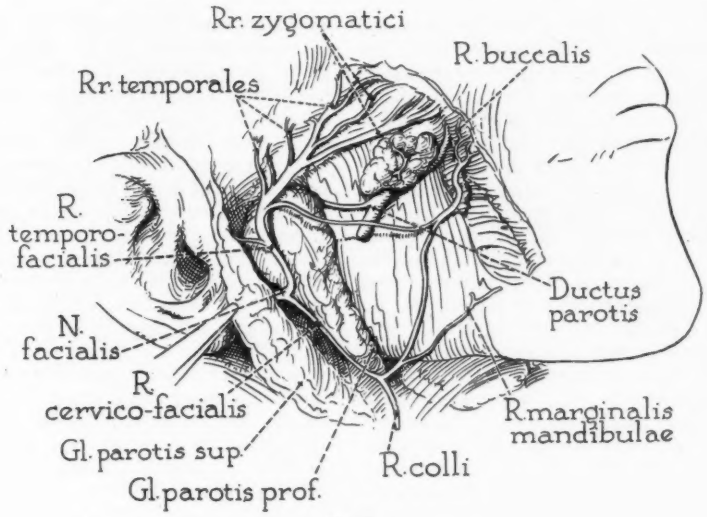

Fig. 6.

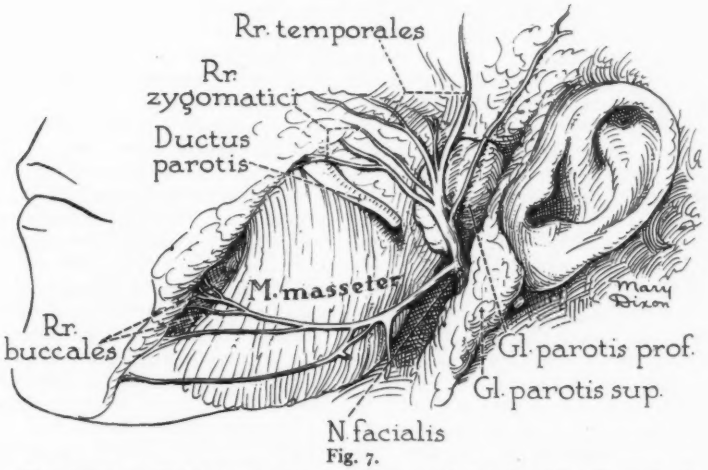

Fig. 7.

Figs. 6 and 7. Facial nerves, deep dissections. Adult male, white. Figure 6, relation of the nerve and its divisions to the "leaves" of the parotid gland; Figure 7 demonstrating the relation of the nonanastomotic type of nerve to the zygoma, mandible, and masseter muscle. In Figures 6 and 7 the parotid duct has been cut.

A. Facial Nerve

After the facial nerve emerges from the skull through the stylomastoid foramen, it passes inferiorly with slight anterolateral inclination, to plunge into the substance of the gland. With the exception of one or two small muscular rami, all of its branches are given off after it has entered the parotid. Regularly the single main trunk splits into two principal divisions, the temporofacial and cervicofacial portions. The point of bifurcation occurs 5 to 7 millimeters dorsal to the ramus of the mandible, where the nerve is entirely surrounded by glandular tissue; in 66 specimens it was found to be a distance of from 1.4 to 4.7 centimeters above the external angle of the mandible, measured along the palpable posterior border of

the ramus (Table I). Most of the specimens fall in a group between 2.9 and 4.4 centimeters (an interval distance of 1.5 cm.); the average measurement is 3.4 centimeters. Converted into a rough measurement of surgical value, the point of bifurcation of the facial nerve lies posterior and slightly medial to the ramus of the mandible and superiorly two-thirds of the distance between the external angle of the mandible and the palpable condyloid process (temporomandibular articulation). Much of the absolute variation in distance is explained on the basis of comparative head size; the greater the cranial and mandibular development, the greater will be the interval.

Of the two principal divisions of the facial formed at the point of bifurcation, the temporofacial portion, supplying the upper part of the face, is by far the larger (Figs. 1 to 7); it is often two to three times the size of the cervicofacial component. The upper division courses anterosuperiorly just below the upper border of the parotid gland; in the first part of its course it lies between the two lobes of the gland (see hereinafter). The lower division arches downward between the two lobes in close association with the posterior border of the ramus of the mandible.

The pattern of branching from the two main divisions which is described in anatomical textbooks, was found to occur infrequently in the authors' specimens. However, the temporal, zygomatic, buccal, mandibular and cervical rami (named on the basis of regional supply) were always identifiable. The scheme of origin, however, varied, and to such an extent that eight general types of configuration could be distinguished (Fig. 8, I to VIII). For purposes of convenience in discussion, these were arranged in the order of increasing complexity, beginning with the simple type regularly described and figured in anatomical textbooks, and ending with those which exhibited a markedly plexiform arrangement. Between these extremes were placed several groups, the selection of which was based upon the number of large anastomoses between branches of one of the two principal divisions of the nerve (preponderantly associated with the temporal portion),[1] and upon the number of anastomoses between the cervicofacial and temporofacial divisions of the nerve. Some of the anastomoses occurred within the gland, others beyond its margins.

Type I (13 specimens, 8 left and 5 right). The basic plan of nerve Type I is simple (Fig. 7; cf. Fig. 8, I). No large unions occur between the various portions of the nerve; rami arise in a spray, and diverge from the two primary portions as blades leave the handle of a fan. Within the substance and close to the border of the parotid gland these fibers are, relatively speaking, of considerable caliber (diameter, 2.0 mm.). They vary in number from four to six at the point of emergence from the gland. The nerves of temporal supply emerge from the superior border of the parotid and arch anteriorly and cranially to reach the musculature of the ocular and temporal regions. The zygomatic ramus, which often includes the buccal supply, courses transversely across the face just above the parotid duct, often crossing it. Either this branch, or more commonly the temporal division, is very large in comparison with the remaining branches. The inferiorly directed cervical and mandibular rami remain hidden between the two lobes of the gland, to emerge finally from the lower pole; the mandibular branch lies along the body of the mandible, or just inferior to it. It is this branch that several surgeons (Bailey, Adson, and Ott) identify first in preparation for total parotidectomy. The cervical portion passes into the platysma muscle. The single major exception to this method of distribution is represented by those specimens of Type I (6 in number) in which a component of the buccal supply passes transversely across the masseter muscle on a level with the angle of the mouth. This buccal component is a very slender fiber, and is not readily found in dissection.

Type II (11 specimens, 5 left, 6 right). The distinguishing characteristic of Type II is the presence of a single anastomosis between the various components of the temporofacial division (Fig. 8, II). In virtually all of the representatives of this group, the temporofacial division quickly splits into two large rami, one directed transversely and the other passing anterosuperiorly. The latter soon further subdivides into temporally directed branches to the muscles below the eye, and a more transversely directed ramus. The middle and lower rami then anastomose at a point 1 to 3 centimeters beyond the anterior border of the gland; from the loop thus formed are given off numerous fine twigs to the buccal and zygomatic musculatures, and less frequently to the temporal region.

In most instances this anastomosis is intimately related to the parotid duct, lying just superficial to it. Rarely (2 cases) the communication occurs within the substance of the gland. From the connecting stem spring the temporal and zygomatic rami, which (as in Type I) are already separate as they pass from the border of the gland. Most infrequently (one instance) the intraparotid loop passes around the superficial temporal artery and

[1] A fact first noted by Tortella (1935).

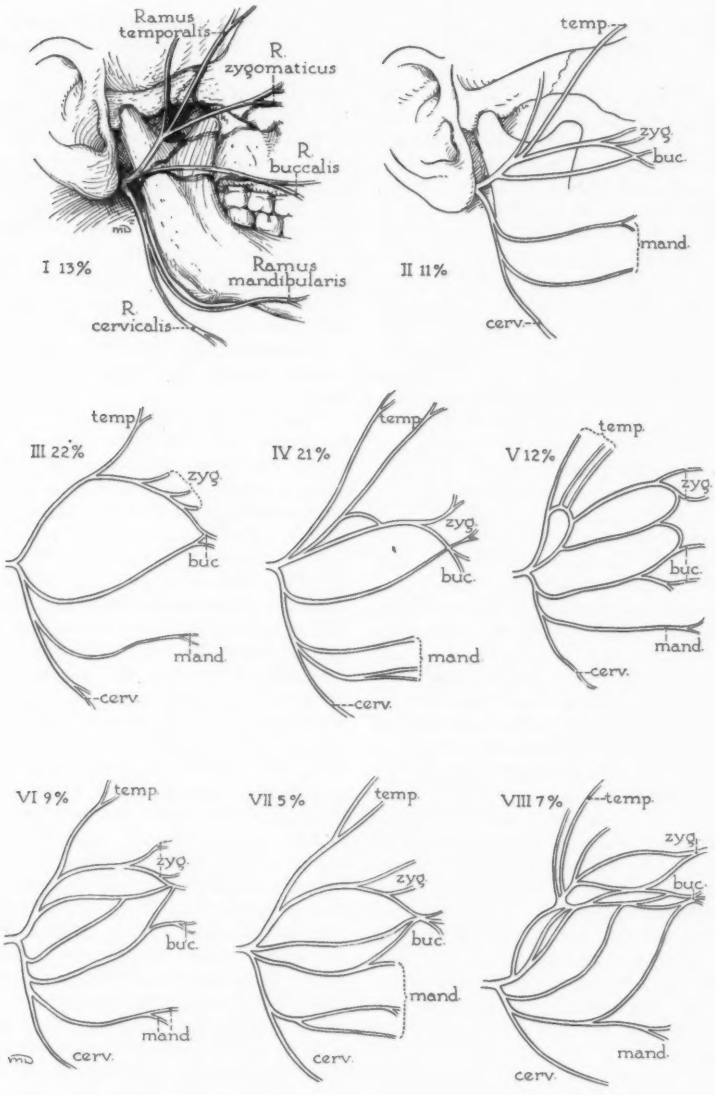

Fig. 8. Major types of facial nerve branching and anastomosis. I, Major divisions (temporal and facial) independent; II, anastomosis between rami of the temporal division; III, connection between adjacent rami from the major divisions; IV, anastomoses representing a composite of those in II and III; V, proximal anastomosis within the temporal component, distal interconnection between the latter and the cervical component; VI, two anastomotic rami sent from the buccal division of the cervical to the zygomatic part of the temporal; VII, transverse ramus, from the trunk of the nerve, contributing to the buccal ramus formed by anastomosis between the two major divisions; VIII, richly plexiform communications, especially within the temporal portion of the nerve.

vein. The inferiorly directed branches in specimens of Type II are similar to the corresponding rami of Type I.

Type III (22 specimens, 9 left, 3 right). This is the third of the groups in which the pattern of configuration of the nerve is of basic character. In the scale of ascending complexity, it represents the first intermingling of elements derived from both of the primary divisions of the nerve, namely, the temporofacial and cervicofacial portions (Fig. 6 and Fig. 8, III). A slender trunk arises from the cervicofacial division very quickly after its origin from the main nerve (within 1.5 cm.) and passes superiorly in an oblique course to anastomose with a strong, arching, continuation of the temporofacial division (Figs. 1 to 3). In all instances the anastomosis is extraglandular, occurring most frequently 1 to 3 centimeters beyond the anterosuperior extremity of the gland. In most instances the anastomosis occurs immediately over the parotid duct, just before the latter passes deeply to pierce the buccal muscles.

In an exceptional specimen (Figs. 1 and 2) the contribution from the cervicofacial division was formed by the union of several filaments.

Type IV (21 specimens, 11 left, 10 right). Type IV is essentially a composite of the two preceding patterns. There is an anastomosis between the temporal and zygomatic subdivisions of the main superior trunk as well as one between the superiorly directed ramus from the cervicofacial division and a strong branch from the zygomaticobuccal supply (Figs. 4 and 5, and Fig. 8, IV). In 6 cases the anastomosis occurring within the temporofacial portion of the nerve was intraglandular, while in the remaining 15 the union occurred beyond the anterior border of the parotid. In 20 cases the anastomosis between the two principal divisions was extraglandular, i.e., having relationships similar to those obtaining in Type III. In the remaining single instance the anastomosis lay between the two leaves of the gland. The latter was the only case among the representatives of Type IV in which both of the anastomoses were entirely intraglandular.

Type V (12 specimens, 6 left, 6 right). In specimens belonging to this group one characteristic feature is the presence, in the temporofacial division of the nerve, of two large anastomoses (Fig. 8, V). The proximal loop is very small and intraglandular; it is usually about 1.5 centimeters in diameter and often encloses the temporal artery and vein. From it arise three major components: small temporal filaments to the muscles at the orbit; a heavier superior branch to the zygomatic musculature; a smaller, somewhat inferior, branch which forms a second loop by joining the preceding over the parotid duct at a point 1 to 3 centimeters distal to the anterior pole of the gland. As the second of two characteristics, this third component is reinforced by an anterosuperior contribution from the cervicofacial division (within a distance of 1 cm. from its source in the main trunk of the nerve). In this way the two main components of the nerve are brought into anastomotic connection. From this distal loop, formed by junction of the two main divisions, small filaments pass the musculature above the angle of the mouth. In only one instance this lower communication was entirely intraglandular; in the remaining 11 the cervicofacial contribution passed beyond the margin of the gland before union.

Type VI (9 specimens, 3 left, 6 right). The pattern in Type VI is the converse of the preceding, in that the arrangement of major and minor loops is reversed. One variable anastomotic loop occurs between rami of the temporofacial division (Fig. 8, VI). In 5 cases, it was relatively small and entirely intraglandular, as in the case of the proximal loop in Type V; in 2 cases it extended less than 2 centimeters beyond the anterior border of the superior portion of the gland; in the remaining 2 (of the total 9) it extended approximately 3 centimeters beyond the border. Additionally, Type VI possesses two anastomotic filaments which pass from the cervicofacial division to intermingle with elements of the temporofacial portion. In 2 instances, these branches arose by a very short common trunk from the cervicofacial division, approximately 1 centimeter beyond the latter's origin. In the remaining 7 a proximal ramus arose about 1 centimeter from the main bifurcation, and a second one was given off at a distance of from 2 to 3.5 centimeters beyond the bifurcation. In 3 cases the latter branch crossed the angle of the jaw. In all instances the rami which arose from the inferior division joined the same transversely directed branch, in succession, 1 centimeter apart, to form an arcade with an arcade. The branch thus contributed to was small, so that the additions gave the appearance of reinforcing it. From the distal loop, which usually lay over the anterior border of the masseter muscle, numerous small filaments passed to superior labial and zygomatic musculature.

Type VII (4 specimens, 1 left, 3 right). This seventh type, while not strikingly complex, was the least common configuration encountered in the entire investigation. It is very similar to Type III in that anastomosis occurs between a strong, transverse branch of the temporofacial

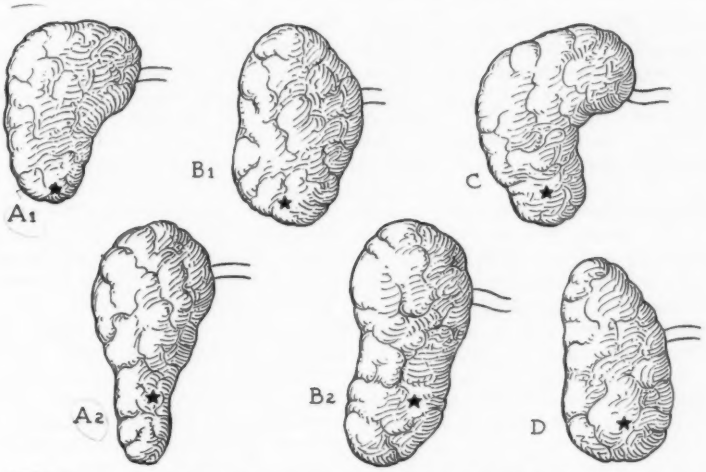

Fig. 9. Types of parotid gland, recording variations in form and size. Star in each indicates the site of the external angle of the mandible.

division with a smaller ascending ramus of the cervicofacial portion of the main nerve (Fig. 8, VII). The unique feature is the presence of a central branch arising from the main trunk of the nerve and passing transversely to join the above-mentioned anastomosis. In this way a third element is contributed to the primary anastomosis. From the anastomosis formed by the union of three branches, numerous terminal filaments arise to supply the musculature between the lower eyelid and the angle of the mouth. The anastomosis bears the usual intimate relationship to the parotid duct, but the point of union is usually situated just inferior to the duct.

Type VIII (7 specimens, 3 left, 4 right). Specimens in this group are characterized by the presence of richly plexiform intercommunications (Fig. 8, VIII). None has a strong transverse branch such as was so commonly present in specimens belonging to the other groups. From 4 to 7 intercommunications occur within the nerve itself, most often between the two main divisions. What the individual rami lack in size, they make up for in number and in frequency of intercommunication. A second striking feature is the presence of small triangular masses of fibrous tissue which occurs between adjacent branches of a nerve. Two of these were found at the first or second branchings of the temporofacial division. They were firmly attached and appeared to be an integral part of the main nervous structure. It is the authors' belief that the presence of such a plexiform arrangement is responsible for the partial successes reported by Duval and Redon (1932) who removed the cervicofacial portion of the nerve in the course of total parotidectomy.[1]

B. Parotid Gland

The parotid gland is an organ of variable form. Despite this fact, the variations can be rather satisfactorily classified (Fig. 9). In addition to the criterion of size, there is that of relative bulk of the superficial and deep portions as discussed by other authors (Grégoire, 1912; McWhorter, 1917). This relationship is also variable, since the deep lobe may be merely a small button of glandular tissue, or may come close to equaling in size its overlying superficial lobe.

The features of form and size were combined in studying 76 glands. The main grouping was made on the basis of form, while subgroups were based upon size. The larger glands (those longer than 6 cm.) extend for a distance of several centimeters into the neck just anterior to the ventral border of the sternocleidomastoid muscle—a fact which is of surgical interest.

Length of gland varies between 4.5 and 9.2 centimeters (average, 6 cm.), while the width varies between 2 and 5.4 (average, 3.3 cm.). More than half of the glands (40 specimens or 52.6 per cent) fall into a group for which a conventional textbook description would be suitable; they are triangular in shape, largest at the superior extremity, and narrowing gradually to a blunt apex

[1] In 5 cases, 2 patients had mouth droop, and 1 had some involvement of the eye; the other 3 were esthetically a success.

pointing inferiorly. Within this inclusive group are two subgroups; the first is made up of small glands (21 in number), whose average length is 5.1 centimeters, and whose average width (at superior pole) is 3 centimeters (Fig. 9, A^1); the second is is made up of glands with average length and width of 6.6 centimeters and 3.4 centimeters, respectively (Fig. 9, A^2).

In the second major group (24 glands, or 31.5 per cent of the total), the gland is not constricted below, but maintains a uniform width throughout its length, with superior and inferior poles gently rounded. Here, again, subdivision on the basis of size can be made: a larger lot (13 specimens), with average length of 5.3 centimeters and an average width of 2.6 centimeters (Fig. 9, B^1); a smaller lot of bulkier glands, averaging 6.5 centimeters in length, and 3.5 centimeters in width (Fig. 9, B^2).

In the third of the main groups (6 specimens) the glands have the form of an inverted letter L (Fig. 9, C); they are almost as broad at their superior extremity as they are long. The average length of these is 5.7 centimeters, while the average width is 4.7 centimeters. The transverse portion of the L, represented by the superior portion of the gland, is made up of glandular tissue which lies along the superior border of the main parotid duct (in 1 instance reaching a length of 5.4 cm.). In all but 2 instances, this glandular tissue was associated with the superficial lobe of the gland. In the 2 exceptions, the tissue was on the same plane as the deep lobe and appeared to be part of it.

In the fourth, and last, category (6 specimens), all of the glands are large, with an average length of 6.7 centimeters, and an average width of 3.7 centimeters. The glands are roughly triangular in outline, but the broad base of the gland forms the inferior pole of the gland, the superior pole then being represented by the rather sharp apex of the gland (Fig. 9, D).

Accessory glandular masses are fairly common; 16 small nodules of tissue occurred in 15 of the 76 cases (19.7 per cent). They are invariably situated superior to the main parotid duct, sometimes partially overlapping it (Fig. 6). Although an accessory gland may be located anywhere between the anterior border of the main gland and the anterior border of the masseter muscle, in the majority of instances they are found along the proximal one-half of the duct. In length the accessory glands vary from 1.0 to 2.3 centimeters (average, 1.4 cm.); in width, from 0.5 to 0.8 centimeter (average, 0.7 cm.). The long axis always corresponds to that of the main duct, into which the accessory element empties by a very short, slender duct.

Regarding the main duct of the parotid gland, it may be said that if it drains the upper portion of the gland, its course will be transverse across the masseter muscle (Fig. 1). Of the glands studied, the duct pursued this course in 42 specimens, a fact which means that in these cases, it was in early close association with the nerves (Fig. 1). When the duct drains the central or the lower portion of the gland, it tends to pass obliquely to the mouth (Fig. 4). Such a course was found in 32 cases. In 3 specimens "double" ducts occurred (Fig. 6). One component drained the superior portion of the gland and passed transversely, while an inferior component drained the lower glandular tissue and coursed obliquely upward. A union occurred between the two elements 1.5 to 2 centimeters beyond the anterior border of the gland.

CONCLUSIONS

So intimate is the relation of the facial nerve to the parotid gland, that the scheme of nervous ramification and intercommunication can be most satisfactorily presented on such basis; in fact, the pattern of anastomosis seems to be governed by the shape and position of the deep lobe of the gland, and by the presence of an isthmus of tissue between the latter and the larger superficial portion.

Although the parotid is subject to considerable variation in size and form, it is invariably bilobed. The small, deep, lobe overlies the condyloid and coronoid processes of the mandibular ramus; it is likely to be ovoid in outline. The large, superficial, lobe, which conceals the lesser lobe, is usually triangular in outline, with the narrowed, bluntly apical, portion more frequently directed downward than upward.

Now, as the trunk of the facial nerve courses toward the surface, through the space bounded by the mastoid process of the temporal bone and the condyloid process of the mandible, it insinuates itself between the lobes of the parotid gland, in close relation to the isthmus. Thereupon it divides quickly, the divisions appearing as the divergent arms of the letter Y; one division ascends obliquely toward the temporal region, while the other descends obliquely into the cervical region. Both of these divisions, and the proximal portions of their branches, are usually covered by the superficial lobe of the parotid; the divisions skirt the corresponding margins of the isthmus, and usually anastomose distally to surround and clasp it. Whether the divisions continue independently or, by conjunction, are circumferential to the isthmus,

they tend to converge as they proceed forward —slightly in the first instance, strikingly in the second. In those cases in which the temporal division joins the cervical (76 per cent of specimens) the fusion occurs in such a way that the buccal branch appears to be the continuation of the confluent portions. The buccal branch is somewhat superior to the main trunk of the nerve (by a finger's breadth or less, commonly), and, even when the superficial lobe of the gland is prolonged forward this branch is likely to be exposed just beyond the parotid's tip. It regularly overlies the parotid duct.

When the divisions remain separate, the branches of the temporal portion spread out like the spokes of a quadrant of a wheel; those of the cervical portion, on the contrary, leave the division as if they were twigs derived from one side of a branch—the division itself continuing, still a prominent branch, into the neck. When, on the contrary, the divisions anastomose, the temporal, zygomatic, buccal and some of the mandibular branches, quit the loop centripetally in series—the lowermost mandibular branch, at least, appearing to be a branch of the descending cervical division, not as a derivative of the loop. Just as there exist variations in the brachial or in the lumbosacral plexus of nerves, here also there are aberrancies in pattern of "cords" and nerves. In about 65 per cent of the cases in which anastomoses occur (76 per cent of the total number), the branches originating from the anastomotic loop are temporal, zygomatic and buccal; in the remaining 11 per cent some mandibular branches are included. This means that in the cranial two-thirds or three-fourths of the entire parotid zone, the related nervous elements are likely to be involved in a plexiform scheme. In most instances the forming elements of the plexus are largely extraglandular.

Secondary anastomotic loops are fairly common, and may be either proximally or distally placed. In rare instances the space enclosed by anastomosis of the two regular divisions (temporal, cervical) of the facial trunk, may be bisected by a third division; this transverse, supernumerary division would seem to be principally buccal, since it reaches the distal (anterior) margin of the loop at the customary point of origin of the nerves destined for the rima oris.

From this anatomical study certain features of a practical significance are made evident; these may be considered in the order in which they would affect the mode of surgical exposure. The parotid fascia should be opened posteriorly and reflected forward from a preauricular incision, in order to expose the anterosuperior, or apical, portion of the parotid gland. Since the gland usually possesses the outline of an inverted triangle, with the base represented by the part of the superficial lobe which coincides with the line of the zygomatic arch, exposure of the gland along its superior margin will lead the operator to its tip. When the apex has, by this maneuver, been uncovered, the parotid duct and the associated buccal branches of the facial nerve can be readily identified, since the duct either extends forward from the apex, or lies just inferior to it. Next, employing the buccal ramus as a guide to the more proximal position of the large temporal division of the nerve, or of the point of anastomosis of the latter with the smaller cervical division, the radially directed nerves can be safely exposed, in serial succession backward, by progressively lifting the margin of the gland. In this process the isthmus, which connects the superficial and deep lobes, will serve as a pedicle, and as a core round which the two divisions course. By tracing the large upper division dorsalward toward the ramus of the mandible, the operator will be guided to the main trunk of the facial nerve. Therefrom, the small lower division can be followed along the inferior margin of the isthmus and downward toward or into the neck. Having thus reached an area where the divisions and rami are strongest and their patterns of branching least complex, glandular tissue may be excised with minimal danger to the facial nerve.

Because the parotid gland is sometimes small, or is so formed as to be constricted cranially, more than the regular fraction of the main divisions may be apparent beyond the periphery of the parotid. Obviously, when such an arrangement obtains, special care must be exercised if the branches are to be spared trauma or transection.

SUMMARY

A study of the facial nerve, especially in relation to the parotid gland, was conducted in 100 carefully prepared dissections of adults.

From the data collected (in the form of artist's drawings and authors' sketches) the bilobed nature of the parotid gland was definitely established, as was also the regular position of the facial nerve between the two glandular portions, namely, superficial larger part and deep smaller portion.

From examination of the collected records of facial nerve ramification, it was found that all could be conveniently and graphically catalogued as belonging to one of a total of eight types, in which those with anastomoses between major divisions or between branches of either of the latter outnumbered the nonanastomotic types in

the proportion of 3:1. It was also learned that in the specimens where anastomosis took place, the loop thus formed surrounded the isthmus of the parotid gland.

The types were illustrated by diagrammatic drawings from actual specimens, and detailed drawings, from similar source, were secured to portray the relationship between the nerve's divisions and branches to the lobes of the parotid gland.

On the basis of the morphological conclusions, some opinions are expressed on importance of the observed facts to procedure in extirpation of the gland. These deal with the manner of reflecting the superficial parotid lobe, the resultant exposure of all larger nervous elements, the existence of an area where nerves are concentrated, the service ability of identifying the common relationship of the buccal component to the parotid duct.

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CAUSALGIA

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THE term causalgia was used in 1865 by Mitchell, Morehouse and Keen to describe a bizarre syndrome resulting from injuries to peripheral nerves. Its cardinal features are the subjective complaint of burning pain, in association with trophic and vasomotor changes in the injured extremity. The pathology and pathogenesis of causalgia are unknown. Indeed, there is some confusion as to what constitutes a case of this condition. Some writers (1, 2, 4) believe that causalgia, Sudeck's atrophy, painful osteoporosis, and other so called "minor causalgias," and, indeed, painful "phantom limb," are different clinical manifestations of the same underlying disorder. The similarity, however, is remote, and we are of the opinion that causalgia varies sufficiently in severity to be considered a clinical entity.

In this paper we will present the data from 15 cases, in which the symptoms and objective findings were of sufficient severity to compare with those described by the original authors. These cases have been studied to correlate subjective and trophic changes with blood flow in the part. Blood flow was determined by means of the oscillometer, skin temperature readings, and at times the histamine flare test. In addition, all patients have had psychiatric examination because of the belief by some that predisposing constitutional psychic factors play an etiologic rôle. The effect of interruption of the sympathetic chain, with procaine block and by surgery, and the effect of hyperthermia, have been observed.

These studies suggest that the pain of causalgia does not result from alteration in the blood flow, for some patients are found in whom the injured extremity is in a state of vasodilatation, while others show vasoconstriction. The trophic changes and the response to heat and cold vary considerably with the blood flow. The severity of trophic changes increases with prolongation of symptoms.

MATERIAL

The 15 cases were encountered in a group of 737 peripheral nerve injuries (2%). The median nerve was involved in 7 cases, the median and ulnar in 1; the brachial plexus (median and lateral cords) in 1. The sciatic nerve was involved in 6 cases. In each instance the wound was of a penetrating type, due to bullet or shell fragment, and was proximal to the elbow or knee. Two patients were officers, 13 were enlisted men. Their ages ranged from 23 to 33 years. The wound became infected in 2 cases. Sizeable foreign bodies were retained at the level of the injury in 3 cases. The nerve lesion was incomplete in each instance. This syndrome has not been seen in any individual in whom the nerve was completely divided. No patients have had any major vascular injuries. Three of the patients had also suffered a concomitant fracture of the femur.

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SYMPTOMS AND SIGNS

Mitchell, Morehouse, and Keen noted that the onset of burning pain was usually late, at times being delayed as much as 1 to 2 months. They observed that pain was always present in the distal part of an extremity, usually in the palm or in the dorsum of the foot, and not confined to the autonomous zone of the injured nerve. They commented that certain patients had warm skin and others, cold, but placed greater stress on the glossy, shining skin, and loss of hair, etc., and considered that these changes would appear in all cases of long duration.

In 9 of the 15 cases here reported, the burning pain was present from the moment of impact. In 3 others it appeared within 24 hours. In 3 it was delayed as long as 3 weeks. The pain was of intense burning character, and varied in intensity with emotional stimuli such as anxiety, anger, or fear. Noises, such as the scraping of a chair, the tearing of paper, loud music, or breaking glass, caused intense suffering. Lighting the room without warning would often provoke a severe paroxysm of pain.

Eleven of the 15 patients obtained some relief from the application of moisture. It was Mitchell's (6) opinion that moisture was the factor which afforded comfort, rather than the temperature. Nine of our patients preferred cold water, 3 obtained some relief from warm water, and in 3 cases the effect of moisture was not significant. Throughout

TABLE I.—SUMMARY OF CASES

Case Age	Injury	Duration	Onset	Relief from moisture	Blood flow	Treatment	Result
1. F.H.M. 26	Bullet, left thigh	3 mo.	Immediate	Warm	Reduced	Sympathectomy, lumbar, L2-3-4	Relief
2. W.W.D. 24	Shell fragment, left thigh	5 mo.	Immediate	Cold	Increased	Sympathectomy, lumbar, L2-3-4	Relief*
3. L.C.K. 23	Bullet, right arm	4 mo.	Immediate	None	Increased	Sympathectomy, dorsal, Stellate and D-2	Relief
4. J.G. 28	Bullet, right shoulder	2½ mo.	Immediate	None	Increased	Temporary relief after procaine block	Relief†
5. A.B. 25	Bullet right arm	7 mo.	24 hours	None	Increased	Temporary relief after procaine block	Relief†
6. J.U. 33	Shell fragment left thigh	2½ mo.	24 hours	Warm	Reduced	Fever therapy, 3 bouts	Relief
7. G.T. 27	Bullet, left thigh; fractured femur	14 mo.	3 weeks	Cold	Increased	Sympathectomy, lumbar, L1-2-3-4	Relief‡
8. G.L. 27	Shell fragment left thigh; fractured femur	7 mo.	3 weeks	Cold	Increased	Sympathectomy, lumbar, L2-3.	Relief
9. D.C. 23	Shell fragment left thigh; fractured femur	8 mo.	24 hours	Cold	Increased	Sympathectomy, lumbar, L2-3	Relief
10. K.S. 30	Shell fragment left arm	2 mo.	Immediate	Cold	Increased	Sympathectomy, lumbar, L2-3	Relief
11. J.L. 24	Shell fragment left arm	3 mo.	Immediate	Cold	—	Sympathectomy, dorsal, preganglionic	Relief
12. B.G. 22	Bullet, right arm	24 hr.	Immediate	Cold	—	Sympathectomy, dorsal, preganglionic	Relief
13. K.M. 29	Bullet, left arm	1 mo.	Immediate	Warm	Reduced	Sympathectomy, dorsal, preganglionic	Relief
14 R.S. 26	Bullet, left axilla	2 mo.	3 weeks	Cold	Increased	Sympathectomy, dorsal, preganglionic.	Relief
15. R.B. 24	Shell fragment right arm	2 mo.	Immediate	Cold	Increased	Sympathectomy, dorsal, preganglionic	Relief

*Prior to neurolysis, warm water afforded relief; after neurolysis cold water afforded relief.
†Spontaneous recovery, but hypersensitiveness to cold.
‡Wound high, right thigh. Removal lumbar ganglia 3 & 4 produced no relief. Removal lumbar ganglia 1 & 2 followed by complete relief.

the course of the disease, in our cases, the patients' demands for cold or hot water did not change except in 1 instance. In Case 2, intense burning pain developed from a partial lesion of the left sciatic nerve above the knee. For 2½ months after injury, at which time neurolysis was done, warm water had afforded some relief. Thereafter warm water was painful but cold water caused marked lessening of pain, and the patient kept the foot immersed in iced water until it was necessary to withdraw it, to prevent vascular damage.

Three patients kept their hands constantly covered with a wet cloth. Another (Case 11) maintained a basin of water at his bedside (Fig 1) for this purpose. Without exception, the patients exercised great care to prevent the part being touched, particularly by rough objects. One (Case 4) kept the hand protected constantly in dry flannel (Fig. 2). Most patients would go to what appeared to be absurd extremes to prevent motion of the part. Some would grasp the painful extremity just proximal to the wrist or ankle with the normal hand, and hold this position for hours. The facial expression usually reflected intense suffering (Fig. 3).

In the more severe cases the patients were poorly nourished due to low food intake, and were irritable and "shut in," showing no interest in family or friends even though they had been overseas for many months. They preferred to be alone in a darkened room. They were unduly critical of attendants. The case histories in most instances revealed items of information such as these, which suggested that the disorder might be entirely psychogenic in character. Mitchell stated that the word "hysterical" seemed to describe the state best.

The motor and sensory loss was difficult to determine, for usually the patient refused to move the part or permit it to be touched. In addition, there was usually marked stiffness of the joints, due to disuse.

Fig. 1. Case 11. Photograph shows method devised by patient to keep hand constantly wet.

Fig. 3. Case 5. Photograph showing facial expression and the patient immobilizing the painful member by holding it with the other hand.

The trophic changes were generally of two types. In the first type, of which we have had 3 cases, the skin was cold, thin, and glistening; the superficial layers were denuded, and sweating profuse. With this there was loss of hair, tapering of the digits, and a tendency of the nails to curl. Oscillometric examinations showed marked vasoconstriction as compared to the opposite extremity, and the skin temperature was from 2 to 6 degrees lower than in the normal limb. The pain was lessened by application of warm water. One case of this type (Case 1) developed intercurrent malaria (Plasmodium vivax). During elevation of temperature he was completely free of pain. This was true with each of the three chills. The pain returned when the malaria was controlled. An additional case (Case 7) was given three bouts of artificial fever therapy, each of 3 hours' duration, with a temperature of 104 degrees. Pain disappeared immediately with the elevation of temperature, and returned in mild form with the fall of temperature after the first two bouts. There was no return of pain after the third.

In the second and more frequent type (9 cases), the skin of the painful part was warmer than that of its opposite member, and the hair long and coarse (Fig. 4). The skin was relatively dry and at times actually scaly. In three instances the skin was smooth, but was not comparable to the glossy skin of those in vasoconstriction. These patients experienced relief from cold water, and the pain was exaggerated by application of heat, either moist or dry. One patient (Case 8), who was placed in a fever cabinet experienced such severe pain that he had to be removed within less than 1 hour. Oscillometric examination on these patients, when it could be done, showed the involved extremity in vasodilatation. The skin temperature of the painful part was from 2 to 5 degrees warmer.

Fig. 2. Makeshift protective covering of dry flannel, constantly worn.

Fig. 4. Case 4. Excessive hair growth is present in causalgic limb.

Fig. 5. Spotty osteoporosis with small bones of painful right foot.

The severity of the trophic changes increased with the duration of symptoms, yet the types seemed unchanged.

In 3 cases, oscillometric and skin temperature studies were not carried out.

OSTEOPOROSIS

In 9 cases the extremities were examined roentgenographically for evidence of osteoporosis. As has been demonstrated by Miller and de Takats, there was spotty osteoporosis of the small bones of the hands and feet in each case with vasodilatation (Fig. 5). If the duration of the illness was long, extending more than 3 months, the demineralization tended to become generalized. The 3 patients who showed vasoconstriction also showed demineralization of the painful part, but it was not spotty.

TREATMENT

Success has been reported with many forms of treatment in causalgia. Mitchell, Morehouse and Keen used leeches. Direct surgical attack on the nerve trunk above, below, and at the level of injury is reported to relieve the syndrome at times. Varying degrees of success have been reported with drugs and physiotherapy. Interruption of the sympathetic chain has consistently been the most efficacious procedure.

Of our cases, one was relieved by fever therapy and two recovered spontaneously. The remainder were treated by interruption of the sympathetic chain. Every patient had repeated procaine block of the appropriate chain. The least number of injections given to one patient was 3, and some patients have had as many as 8. The relief following injection was dramatic. It was instantaneous and absolute, and usually was maintained for intervals of from 1 to 3 hours, after which the pain returned, reaching its maximum intensity within a short while. We have not been able to provide any lasting benefit by this procedure, and have subsequently interrupted the sympathetic chain with surgery. Despite this brief period of complete relief, the patient almost invariably objected to repeating the procedure, because of fear of being "stuck."

Cervicodorsal sympathectomy was done on 1 case in which the arm was involved, the stellate and 2nd dorsal ganglion being removed. Six cases with arm involvement were treated by preganglionic ramisectomy.

In 5 of the 6 cases in which the leg was involved, the 2d, 3d and 4th lumbar ganglia were removed. Four were entirely free of pain upon awakening from the anesthetic and have remained well to this date. In 1 case (Case 8), removal of the 3d and 4th lumbar ganglia only was done at an initial operation, because of technical difficulties, and pain persisted. Subsequently the 1st and 2d lumbar ganglia were removed, with complete relief.

Neurolysis was done in 5 cases, and periarterial sympathectomy at the level of the injury in 3. The pain was not influenced by these procedures.

It was impressive to observe the remarkable change in the patients' attitude and behavior following relief from pain. Without exception they became pleasant, co-operative, and happy, and showed interest in their families and friends. In several instances the recovery of function after sympathectomy was rapid, suggesting that reflex paralysis was present. In many the nerve injury was mild, and the ultimate recovery after sympathectomy was good. Each patient in this series, however, was left with a rather marked hyperesthesia in the autonomous zone of the involved nerve. During the period of pain the patient would not move the part, and the joints stiffened rapidly. In the majority of instances this was the chief residual disability. The stiffness was more marked in those cases of long duration.

PSYCHIATRIC ANALYSIS

Each patient of this group was submitted to a psychiatrist for examination after being relieved of the pain, and each one was classified as a nor-

mal individual with a stable personality. Six patients were returned to duty, 4 were discharged for residual disability of the injured nerve but without pain. Five are still under observation.

ANALYSIS OF STUDY

The material on which this paper is based is not sufficient to permit final conclusions. It is possible that additional observations will show that the trophic changes are not always consistent with the alterations in blood flow, as we have observed. It is also possible that the blood flow in a causalgic limb may vary from time to time, but this has not been observed.

The permanent relief of pain which accompanies interruption of the sympathetic chain suggests that the mechanism of relief is by interruption of an afferent pain pathway. The relief of pain which accompanies the application of warm or cold moisture distal to the injury and the relief accompanying hyperthermia, however, is not consistent with this argument and is not understood.

The personality changes always present during the painful stages are secondary to the pain. There is no evidence in our cases that there is a predisposing constitutional psychic factor.

SUMMARY AND CONCLUSIONS

In a study of 15 cases of causalgia the following observations were made:

1. Burning pain is a constant complaint and is usually immediate in onset.

2. The median or sciatic nerve was involved in each instance, and the lesion was incomplete.

3. Certain patients showed vasoconstriction in the causalgic limb; others showed vasodilatation.

4. The trophic changes and response to warm or cold moisture and to hyperthermia varied depending upon the blood flow.

5. Twelve patients were relieved by sympathectomy of the involved limb; 1 was cured by artificial fever therapy; and 2 recovered spontaneously.

6. Further observation as to the value of fever therapy will be made.

7. Direct surgical attack (neurolysis) upon the injured nerve which was performed on 5 cases, and periarterial sympathectomy at the level of injury, performed in 3, have not been of benefit.

8. Procaine block of the sympathetic chain affords complete relief temporarily and should be repeated 2 to 3 times, although no case in this series has had any lasting benefit from this procedure.

9. Sympathectomy (preganglionic) gave immediate and lasting relief to 12 patients.

10. The site of injury must be included in the sympathectomy.

11. Sympathectomy should be done early to prevent stiffness of joints due to disuse.

12. The personality changes always present during the painful stages are secondary to the pain. There is no evidence in our cases that there is a predisposing constitutional psychic factor in causalgia.

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A SAFE, SIMPLE AND EFFICIENT METHOD OF INTESTINAL ANASTOMOSIS

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NO one single method solves the problem of how best to do an intestinal anastomosis. Many fine methods, some extremely ingenious, have been described and all have their good points and probably all are equally efficient in hands trained to use them. Most require specially designed instruments in addition to special skill in the use of these instruments.

However, it is one thing for an expert surgeon, thoroughly trained and adequately equipped, to elect to do a resection and anastomosis, and for an unskilled surgeon who operates only occasionally to be suddenly confronted with the necessity of doing one as an emergency. Many emergencies require resection, and many such cases are handled by surgeons neither trained nor equipped to do a resection. It seemed to me that if a method of anastomosis could be worked out whereby only the ordinary instruments found on the usual hospital tray were necessary, many more surgeons might be able to make use of it. The method to be described was therefore devised. The operation can be readily carried out with the use of only standard hospital instruments. The method is almost fool-proof even for those of little training if the steps are carefully carried out. Recently Stevenson and Totten have published descriptions of two other methods designed probably with the same thought in mind; careful study of these articles is recommended.

TECHNIQUE

Instruments. Either long Kocher or straight Ochsner hemostats are used. I use two long Ochsner hemostats with the end teeth filed smooth (Fig. 2, insert) although this is not essential. A small rubber tubing screw clamp is used to hold the forceps together (Fig. 6, insert, *A*) while the anastomosis is completed. This clamp is found in every hospital intravenous set and does not have to be of the design shown here; any small tubing clamp will do. A few curved Kelly or mosquito hemostats are useful. No. 0 chromic catgut sutures on straight atraumatic intestinal needles are used. For the outside or last row of sutures, a long thread with an atraumatic needle on each end is useful but not essential.

Read before the Texas Surgical Society, Galveston, Texas, October 3, 1944.

Procedure. Step 1. The segment to be removed is determined, and the lines of section are chosen. At these two points a blunt hemostat is pushed through the mesentery, and a hole is made which is enlarged toward the diseased segment (Fig. 1). Enough mesentery is denuded so that the area for anastomosis will be mesentery free. The hemostats (crushing) are so applied that the mesenteric border comes to the center of the crushed area, not at one end of it. The hemostat therefore is applied at right angles to the mesentery (Fig. 2), not parallel to it. Totten is, I believe, the first to describe this step and deserves credit for so doing, but I have been using it for some time. Two heavy straight hemostats are also placed on the diseased segment, which is then cut away with a cautery as usual. We now have the situation as shown in Figure 2.

Step 2. With a straight intestinal needle, a through-and-through suture is placed across the end of each bowel end (Fig. 3). This suture passes through and through from side to side, just as closely below the hemostat as possible but does not pass over it. It is most convenient for the operator holding the hemostat in his left hand, to start the suture at the end of the hemostat and sew toward the handles. The first and last bites must be taken in the very edge of the bowel itself. Each bowel end is so treated.

Step 3. Each hemostat is taken off (Fig. 4) and carefully reapplied (Fig. 5) so that its tip end is not quite level with the edge of the bowel wall (Fig. 5). The hemostat is reapplied in the original crushed area, and its tip must catch the end of this first suture which is cut short after being caught in the end of the hemostat (Figs. 5, 6). The reapplication of the hemostat is an important step.

Step 4. The hemostat blades are laid side by side and held together with the screw clamp (Fig. 6). To avoid having any space between the distal ends of the hemostats, a small piece of metal bent on one end (Fig. 6, insert, *B*) is used to pry the handles apart. A sterile tongue blade, always available, will serve the same purpose. If the hemostat blades are long enough the screw clamp

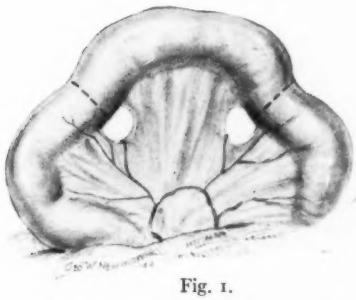

Fig. 1.

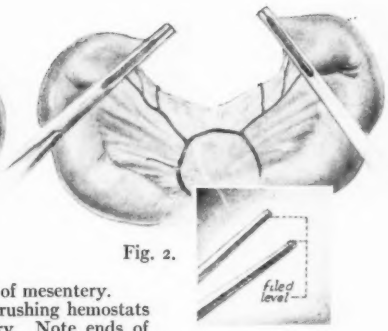

Fig. 2.

Fig. 1. Area of anastomosis denuded of mesentery.
Fig. 2. Diseased portion removed. Crushing hemostats are placed at right angles to mesentery. Note ends of hemostat projecting slightly beyond bowel walls. The insert shows ends of Ochsner hemostat filed smooth.

can be applied distal to the lock, thus making possible exact approximation of the blades. Like Totten I had had a special holding device prepared, but this simple screw clamp is far superior. The operation can be done without the use of the screw clamp but with it the procedure is materially simplified.

Step 5. Suturing is now begun. Interrupted mattress sutures are used, the first being placed so as to cover the ends of the hemostat. Unless the hemostat has been pulled back and reapplied, as described in Step 3, the ends would have to remain protruding. These mattress sutures are placed about halfway up the clamps (Fig. 6) and tied (Fig. 7).

Step 6. At this point the hemostat is rotated 180 degrees, and half of the posterior side is likewise treated (Fig. 8).

Step 7. The hemostat is rotated back to its original position, the screw clamp is removed, both blades of the hemostat are loosened and pulled back enough so their ends are only halfway across the crushed area and just under the last tied stitch. They are then reapplied and the screw clamp again put on (Fig. 9).

Step 8. The anterior row of sutures is now completed, the hemostat rotated again and the posterior row also completed. As the last mattress suture is made ready to tie, the clamp and hemostat are loosened and pulled out completely (Fig. 10).

Step 9. With a long thread of No. 0 chromic and an atraumatic needle on each end, a running suture is placed completely around the anastomosis. This row of sutures is started at the point where the short ends of the first sutures are located, half of the suture material being used for the anterior, half for the posterior, layer (Fig. 11). This is tied.

Step 10. The original through-and-through sutures across both bowel ends are now grasped by the long ends, which were left uncut when inserted, and are pulled out. Until these sutures are pulled out no spillage from either bowel end could occur accidentally, even if the bowel end should pull out of the holding forceps as occasionally occurs.

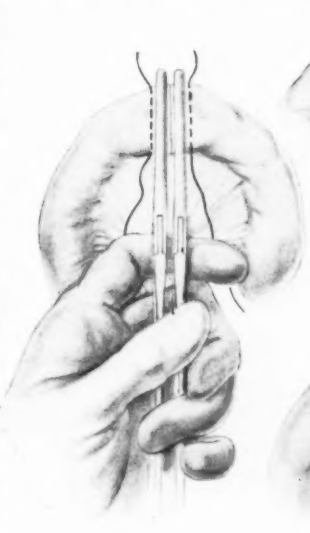

Fig. 3.

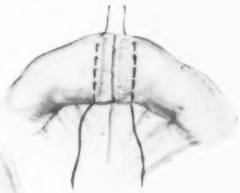

Fig. 4.

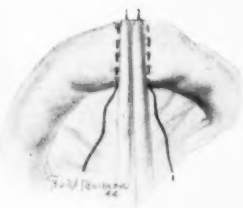

Fig. 5.

Fig. 3. Through-and-through sutures in place across each bowel end.
Fig. 4. Hemostat momentarily removed.
Fig. 5. Reapplication of hemostat. Note that ends of instrument do not go quite to extreme edge of bowel wall, and that short end of suture is caught in blades at tip.

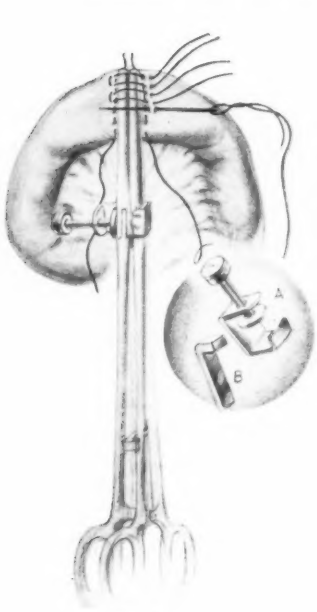

Fig. 6.

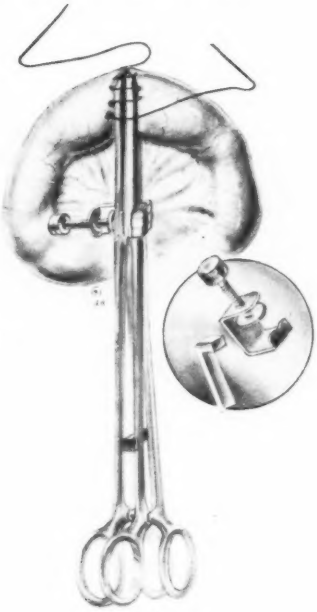

Fig. 6a.

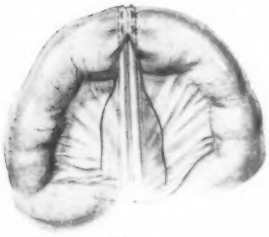

Fig. 7.

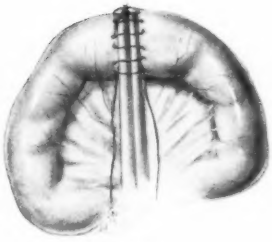

Fig. 7a.

Figs. 6a to 10a, inclusive, show method of anastomosis by using continuous suture for the first layer, mattress sutures for the second.

Fig. 6. Placing of anterior sutures. The first stitch should cover ends of clamps. Note screw clamp in place at clamp locks, and use of wedge between handles eliminates space between clamp blades. Insert shows clamp and wedge.

Fig. 7. First half of anterior row completed.

Sutures must be placed deeply enough to catch the submucous layer. Failure to do this may and often does result in leakage. When the needle point is placed deeply enough as the suture is started, the bit of tissue over it is white and blanched as upward pressure is made. If one can see the needle point all the time it is not deep enough.

Some prefer to use a running stitch as the first row, instead of the interrupted mattress sutures. This is very easy to do with this technique, and is shown in Figures 6a, 7a, 8a, 8b, 9a, 10a, and is somewhat faster. I would call attention at this point, however, to the very great importance of placing the interrupted mattress sutures *first*. By so doing the danger of any pursestring effect is obviated. When the running suture is used as the first row, the pursestring tendency which develops as the suture is drawn taut is difficult to prevent. The method recommended offers considerable protection against this tendency to contract and reduce the diameter of the anastomosis.

Several steps of prime importance are worthy of mention:

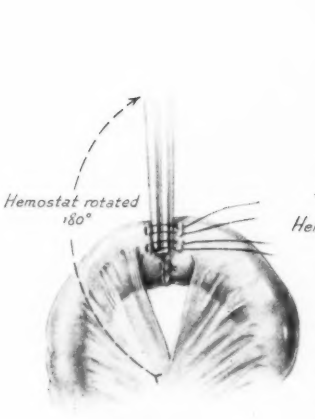

Fig. 8.

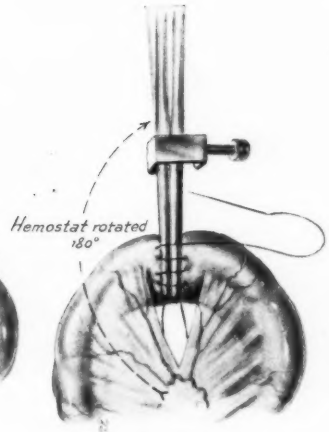

Fig. 8a.

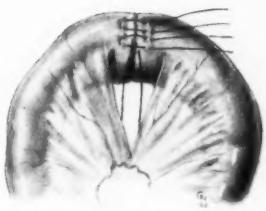

Fig. 8b.

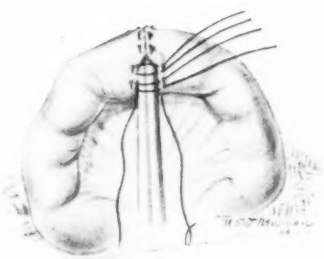

Fig. 9.

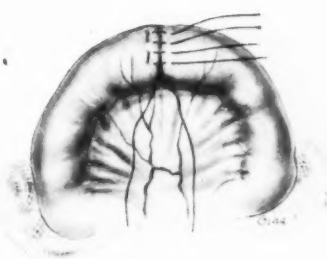

Fig. 9a.

Fig. 10.

Fig. 10a.

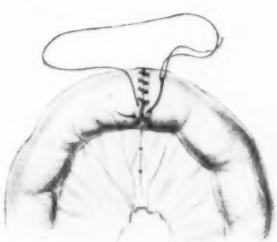

Fig. 11.

Fig. 8. Hemostat is rotated; first half of posterior row of sutures is placed and tied.

Fig. 9. Hemostat has been rotated back to original position, loosened, pulled back so that ends are just under last tied anterior stitch, reapplied and rest of anterior row of sutures is placed and tied. Hemostat is then rotated again to position as in Figure 8, and rest of posterior row is completed, after which hemostat is withdrawn completely.

Fig. 10. First row of sutures is completed. Note the two original through-and-through sutures still in place. They can be removed now or after the running stitch is placed.

Fig. 11. Placing of the last row of sutures, continuous.

1. The hemostats are so applied that the mesentery comes to the middle of the hemostat.

2. The portion of bowel to be used in the anastomosis must be denuded of mesentery.

3. A through-and-through suture in each bowel end, if used as described, absolutely prevents any accidental spill *at any stage* of the operation even if the bowel end drops out of the clamp.

4. The method of loosening and reapplying the clamps permits more accurate placing of the sutures, with the turning in of the minimum amount of bowel end. If a very thin bladed hemostat had the rigidity of the heavier ones, this step might be avoided.

5. It is important that every stitch must catch up the submucosa if it is to have any holding power.

6. The use of interrupted mattress sutures as the *first* layer is urged because they prevent the pursestring effect accompanying the use of a continuous stitch as a first layer.

7. The method described is simple and safe. It is not aseptic, only relatively so. It requires no special instruments or training, and by the use of a simple screw clamp the services of an experienced assistant are not essential.

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TRANSVERSE UPPER ABDOMINAL INCISIONS

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THE transverse upper abdominal incision has many advantages over the longitudinal rectus muscle splitting incision for upper abdominal surgery. These advantages are: (1) the blood supply of the abdominal wall is interfered with but little; (2) the nerve supply of the abdominal wall is not damaged; (3) the wound tends to come together naturally; (4) postoperative distention, if present, puts much less strain upon the wound than when a longitudinal incision is used; (5) patients resist deep breathing much less and thus the incidence of postoperative pulmonary atelectasis is lessened; (6) it affords better exposure of the upper abdomen with less necessity for the packing away of the small bowel; (7) wound disruption is less frequent and more readily repaired when it does occur; (8) the danger of postoperative hernia is less; (9) patients may be allowed out of bed very early because the sitting or upright position decreases rather than increases the strain on the wound.

The transverse upper abdominal incision also has certain disadvantages: (1) it is more time-consuming; (2) in some cases, if an appendectomy is to be combined with an upper abdominal procedure, it may be difficult or occasionally impossible to accomplish this step through the upper abdominal incision; (3) in some cases, in the presence of a narrow subcostal angle, the exposure is no better than it is through a longitudinal incision; (4) in cases of total gastrectomy while some operators believe that the high left rectus muscle splitting incision gives better exposure, others do not concur in this opinion; (5) cutting across the rectus muscle transversely appears to be physiologically unsound, and it is because of the fear of possible irreparable damage which may follow that many surgeons prefer not to use this incision.

From the Division of Surgery, University of Oregon Medical School.

In order to learn what actually happens to the cut ends of the muscle, we made a study of the results in dogs of cutting the rectus muscle transversely and resuturing the fascia without suturing the muscle. After a 2 month interval we reopened the wound and found the muscle densely adherent to itself at the cut ends and also to the overlying and underlying sheath, which, in effect, gives an additional inscriptio tendinea in the muscle.

A study of microscopic sections revealed that the cut ends of the muscle showed the same kind of healing as was found after the use of the muscle fascia suture as done by Koontz, and by Rosenblatt and Cooksey, namely: a connective tissue union occurred between the two cut ends of the

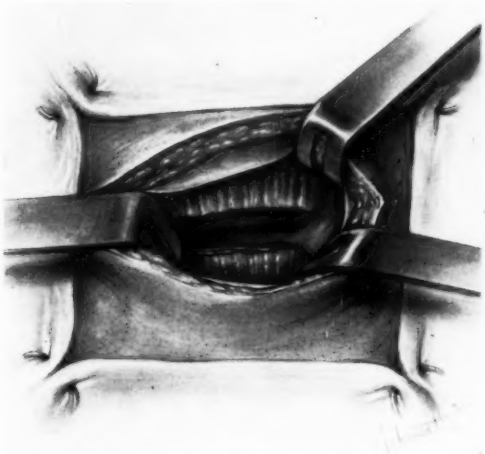

Fig. 1. Transverse incision of rectus muscle of dog.

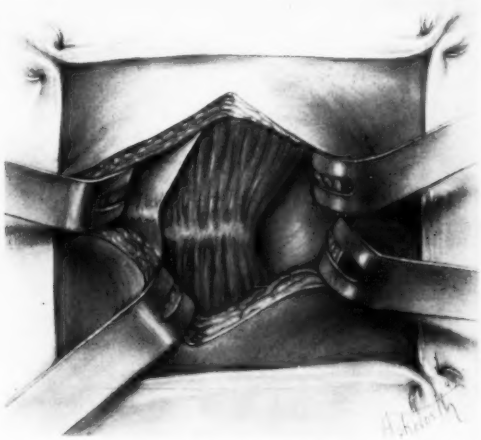

Fig. 2. Healing 2 months later.

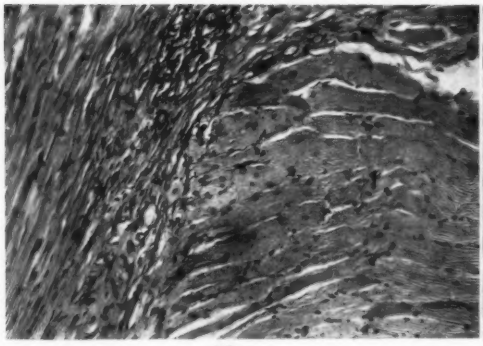

Fig. 3.

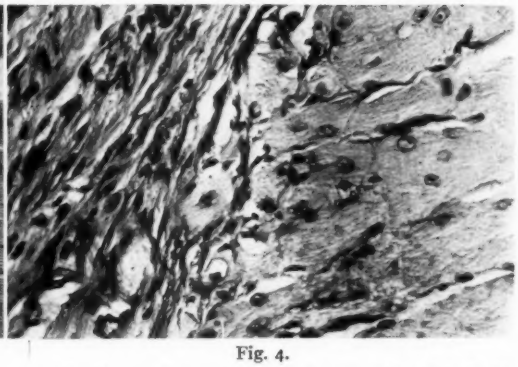

Fig. 4.

Fig. 3. Type of union at cut edge of muscle.
Fig. 4. Higher power photomicrograph showing connective tissue cells in and around the muscle interlaced with fibrous tissue bridging the muscle gap.

muscle. White fibrous connective tissue cells were always present in the muscle because the muscle bundle was surrounded by a sheaf of white fibrous connective tissue and each muscle fiber was surrounded in a like manner and the entire muscle or group of muscle bundles was also held together by connective tissue cells. These elements from both sides join and make a very firm union due to the fact that the connective tissue elements are anchored like tentacles in and around the muscle fibers and bundles.

A study of the accompanying photomicrographs will demonstrate the presence of the endomysium, perimysium, and myomysium (the connective tissue cells around the muscle) and the hundreds of interlacing strands of connective tissue which in this manner anchor the cut ends of the muscle together. In general, from our study, we are convinced that very firm and satisfactory healing of the cut muscle occurs and that the union thus formed is fascial in character and equivalent to an additional inscriptio tendinea.

In summary, we believe that for many cases the advantages of the transverse upper abdominal incision outweigh its disadvantages. The point of view that cutting across the rectus muscle may lead to difficulties in healing is only psychological, as is evidenced by the type of union obtained in this study.

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PRIMARY TUMORS OF THE LIVER

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THE paucity of recent literature on the subject of primary tumors of the liver and the futility with which such tumors are usually regarded are indicative of the need for pointing out favorable aspects in order that patients who would benefit by surgery will not be denied early adequate treatment.

An outline of primary tumors of the liver, excluding tumor-like hyperplastic nodules and secondary tumors, will serve as a basis for discussion of diagnosis and treatment.

TRUE PRIMARY TUMORS

1. Hepatomas
   a. Liver cell adenomas
   b. Liver cell carcinomas with or without cirrhosis
2. Cholangiomas
   a. Adenomas of intrahepatic bile ducts, solid or cystic
   b. Carcinomas
3. Cholangiohepatomas of both liver cell and duct elements
4. Tumors primary in the liver but not of specific hepatic elements (vascular, fibrous, adrenal rests, etc.).

Adenoma is limited to benign encapsulated tumors of glandular origin and hence excludes all those with blood vessel or regional invasion, and those with metastasis. This eliminates such paradoxical terms as "malignant adenomas."

Some authors (Benson and Penberthy) would separate the smaller slowly growing benign rests of liver cells from adenomas by calling them hamartomas. However, they resemble adenomas in appearance and when large enough to be manifest they behave like adenomas clinically, requiring the same kind of treatment, and hence there is no practical advantage of attempting a separate classification of hamartomas.

The hyperplastic nodules of multiple foci of regeneration in cirrhotic livers do not meet the criteria of adenomas. They are without true capsules and are only surrounded by condensation of fibrous tissue of the cirrhotic process. They are not autonomous, for their physiologic secretory activity corresponds to that of the rest of the liver and through functioning duct system it is drained with that of the liver as a whole.

Adenomas of liver cells grossly are isolated, encapsulated masses of atypical cells arranged in cords with intervening blood sinusoids, but with no bile ducts or portal triads. The uniform large cells have eosinophilic granular cytoplasm and central nuclei, usually single but at times multiple, with minimal proliferative activity and no hyperchromatism. There are no signs of peripheral nor blood vessel invasion and metastasis does not occur from these benign lesions (see Figure 1, a and b, of a benign adenoma that was resected).

Carcinoma of liver cells is characterized by increased proliferative activity resulting in smaller cells with less cytoplasm, loss of granularity, a change from eosinophilic to basophilic staining quality, and nuclear hyperchromatism accompanied by rapid proliferation by amitosis or atypical mitosis. There are no signs of secretion such as gross bile staining or microscopic plugs of inspissated bile nor is there time for calcification of necrotic portions of the tumor as there is in adenomas. Typical lesions of each class are easily recognized but the borderline types cause difficulties in determining the exact pathologic significance and therapeutic requirements.

Cholangiomas are more easily classified into benign or malignant types of either cystic or solid tumors.

Primary tumors from nonspecific elements in the liver, such as vascular or stromal tumors, do not differ pathologically from similar tumors in other parts of the body and hence need no special mention.

CLINICAL DIAGNOSIS

Low incidence of primary tumors of the liver is not conducive to frequency of correct diagnosis. At the Cincinnati General Hospital there were 353,971 admissions from 1916 to 1941, inclusive. These admissions were typical of a general hospital and include minor cases as well as readmissions. A total of 73 cases were clinically diagnosed primary carcinomas of the liver on the basis of symptoms and signs as well as x-ray and laboratory studies. However, only 43 cases had microscopic studies, which showed the clinical diagnosis to be correct in 31 cases and incorrect in 12. This proportion of incorrect diagnoses indicates the clinical error to be 20 of the 73 cases, leaving 53 probable cases or an incidence of 0.015 per cent of total admissions as cases of primary carcinomas of the liver. With a much greater incidence in tropical countries the proportion of correct clinical diagnosis is higher (Tull, Strong, and Pitts).

Dr. Warvi was killed in an automobile accident after receipt of this manuscript.

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TABLE I.—FREQUENCY OF SYMPTOMS AND SIGNS IN PRIMARY CARCINOMA OF THE LIVER

Symptoms and signs	37 proved cases of C.G.H. Per cent	500 proved cases reported in literature Per cent	134 cases reported by Tull Per cent
Anemia	97	68	38
Weakness and weight loss	94	88	88
Palpable tumor	91	68	68
Jaundice	80	34	34
Pain	71	52	10
Fever	52	34	38
Vomiting	44	12	2
Edema of legs	40	60	84
Ascites	37	46	48
Fixed diaphragm	18	30	38
Tender liver	15	17	15

Adenomas of the liver can be diagnosed clinically by symptoms and signs that are of longer duration before the patient finds it necessary to come for treatment and more localized in the right upper quadrant than carcinoma. The presence of an upper abdominal mass and a sensation of fullness or dragging is usually the first manifestation of an adenoma noted by a patient, in contrast to the distinct pain of carcinoma. Local obstructive manifestations affecting the gastrointestinal tract, bile ducts, or portal circulation, causing vague indigestion, vomiting, jaundice, or ascites are more prominent and may eventually cause death without the systemic disturbances of carcinoma and its metastases. Fever is exceptional in adenomas and present only in large ones undergoing necrosis, but is reported present in at least half of carcinomas. Cystadenomas have the signs of a cystic tumor in addition to the manifestations of a mass crowding surrounding structures and hence is more easily differentiated from malignant growths but other lesions must be considered.

Symptoms and signs of primary carcinoma of the liver are given in Table I.

The variations in the percentage of occurrence of manifestations of carcinoma of the liver in the table are indicative of the difference in the behavior of the type of carcinoma predominating in various geographical locations. The symptoms and signs of anemia, palpable tumor, jaundice, pain, and vomiting, are associated with tumors of longer duration and of larger size as in our cases, while those of weakness, weight loss, fever, peripheral edema, ascites, and fixed diaphragm are present with rapidly disseminating and invasive tumors such as in Tull's cases. The manifestations in the total 500 cases represent more of an average of symptoms and signs, including those of the highly malignant ones occurring in Asiatic countries as well as those of lower malignancy reported from Europe and America. Bile duct carcinomas of the liver tend to be more malignant with symptoms and signs of greater severity than those arising from liver cells. In our cases, 9 were of bile duct origin with an average survival of only 1½ months from the onset of symptoms to death, in contrast to an average of 8 months' survival in 22 cases of carcinoma of liver cells.

Unusual symptoms and signs have been reported such as those of an acute abdominal accident when spontaneous rupture of a necrotic tumor causes intraperitoneal hemorrhage (Binkley). The pain, fever, and hematemesis from associated esophageal varices adds difficulties to diagnosis of some carcinoma cases. Adhesions about an adenoma may simulate the fixation of carcinoma and can be differentiated only by exploratory laparotomy (Farani).

Laboratory studies as a rule do not aid in differential diagnosis but are essential in determining physiologic disturbances to be corrected before operation. One exception is when a tumor is found associated with jaundice. Then the laboratory findings of acholic stools, absence of urobilinogen and direct van den Bergh differentiate obstructive jaundice suggestive of a large adenoma rather than the hepatic failure of carcinomatous involvement. An anemia must be corrected preoperatively. Prothrombin and bleeding time should be returned to normal. Low results in liver function tests (Bargen and Rankin, Cohen and Hekhuis, Moranze, Moranze and Rothman) and the presence of "hepatic hypoglycemia" would indicate extensive liver damage due to an inoperable tumor.

Biopsy is imperative in diagnosis of liver tumors and it can best be obtained during an exploratory laparotomy, permitting inspection of the tumor for extent of involvement, invasiveness, cellularity, presence of encapsulation or of metastasis. No alarming bleeding has occurred if hemostatic sutures are placed in readiness before the excision of an adequate wedge of liver tissue. Peritoneoscopy also offers some opportunity to determine operability in addition to obtaining biopsy for microscopic study (Beling). Aspiration biopsy is reported to give 73.5 per cent correct diagnoses of liver tumors at Memorial Hospital at New York. Punch biopsy has a few advocates.

Diagnostic accuracy in reported cases of resected tumors of the liver is difficult to ascertain, for from a total of 224 cases reported completely enough to tabulate the method of resection, results, and pathologic diagnosis, only 45.1 per cent gave a definite preoperative clinical diagnosis. However, most of those not stating a definite

TABLE II.—DIFFERENTIAL DIAGNOSIS OF LIVER TUMORS

Means of manifestation	Benign	Primary malignant	Secondary malignant
Symptoms	Primary of pressure as vague local distress, indigestion or gastric or duodenal displacement	Definite pain with invasion. Systemic symptoms with anemia, weakness, anorexia. Hemoptysis from esophageal varices or gastric invasion	Symptoms of tumor elsewhere that may be smaller than the liver metastasis. History of removal of possible primary
Signs	Palpable abdominal mass is firm, movable, solitary and rarely tender	Tumor mass is fixed, hard, multiple and often tender	Discovery of tumors elsewhere often with little symptoms
Laboratory	Jaundice, obstructive, if bile duct occluded. Acholic stools. No urobilinogen. Van den Bergh immediate direct. Otherwise physiology undisturbed	Jaundice of hepatic failure with invasion. Stools ± acholic. Strong urobilinogen. Van den Bergh is indirect. Anemia. Hypoproteinemia	Tests for significant disturbances with tumor elsewhere as in urinary, gastrointestinal tract, bone marrow, etc. Anemia. Hypoproteinemia
X-ray	Localized mass in liver displacing other organs as stomach or duodenum	Invasive, fixed mass in liver. Diaphragm elevated and often fixed	Search for tumor elsewhere as gastrointestinal tract, etc.
Biopsy	Visualization to show accessibility for resection	Visualization of invasion, multiplicity. Rarely resectable	First of all possible sources including suspicious nevi. Later of liver mass to discover its source

diagnosis carried out therapeutic measures which leaves one to assume a correct preoperative diagnosis was made. Hence the results can be stated thus: Preoperative diagnosis was correct or not stated in 73.2 per cent; preoperative diagnosis was wrong in 26.8 per cent.

At the Cincinnati General Hospital, 47 cases of clinically manifest adenomas and carcinomas of liver cells have been studied microscopically. Of these 33, or 70 per cent, had a correct clinical diagnosis before operation or autopsy.

Differential diagnosis is admittedly difficult but often possible when all factors are considered together and for that reason the following diagnostic table is included.

TREATMENT

Adequate noninjurious hemostasis has been the major problem in surgical treatment and the subject of experimental work. That success experimentally is no guarantee against failure when applied clinically was shown as early as 1879 when Tillman controlled bleeding with ease by simple pressure after ligation of major cut vessels in resected livers of animals. Attempt by Escher to apply this clinically resulted in fatal hemorrhage. The human liver with a pathologic lesion differs by being abnormally friable and highly vascular. Tamponade in various forms, application of hemostatic substances, and reduction of blood supply by tourniquets or clamping about the liver or hepatoduodenal ligament are not entirely successful. Cautery hemostasis proved useful only when it was controllable as by electrocoagulative methods. Hemostatic sutures proved most effective experimentally as well as clinically. Substances used to prevent sutures from cutting into liver tissue have not proved practical. The introduction of blunt needles that push aside blood vessels rather than penetrate them with consequent bleeding was a real contribution by Kousnetzoff and Pensky.

Indications for surgical removal of primary tumors of the liver depend upon their size, their location with relation to major bile ducts and blood vessels at the hilum of the liver, and upon the general condition of the patient including the condition of the rest of the liver. The majority of authors (Scheleff, Tinker, Gray, Cullen, Tuffier, McArthur, Fevre and Dassios) believe resection is indicated in adenomas, cystadenomas, localized solitary carcinomas, and hemangiomas but with the following restrictions: no lymph node metastasis should be demonstrable as in the regional nodes along the vessels at the liver hilum, the tumor should not involve the major blood vessels nor bile ducts at the hilum (Ward), and there should be no marked reduction of hepatic function indicative of extensive involvement of the liver parenchyma (Walton, Nadler, and Wolfer). In addition, in cases of cystadenomas one must decide whether to marsupialize or resect completely and also one must rule out generalized cystic disease that involves other organs as well. There are surgeons with two extremes of opinions: those who believe surgical intervention is very rarely feasible (Crile, Cole, Alessandri) and those who optimistically resect extensive primary carcinomas with involvement of adjacent organs or even known secondary carcinomas (McArthur, Cattel, Cullen). At the Cincinnati General Hospital an exploratory laparotomy is done when symptoms, signs, x-ray and laboratory findings are those of a freely movable tumor of the liver without evidence of metastasis, without marked hepatic insufficiency and without a grave operative risk. Actual resectability can best be determined during the exploratory laparotomy.

Preoperative preparation of the patient must be directed toward the improvement of the liver status and its related alterations when it is damaged as well as of the general status of the patient. Vitamin K should be given in jaundiced patients with bleeding tendency and low prothrombin levels. Carbohydrates reduce fatty infiltration of the nonneoplastic portion of the liver and increase the organ's tolerance to the injuries of operation (Ravdin). Because of the susceptibility of the liver to anoxia all possible respiratory diseases, low hemoglobin, cardiac decompensation and histotoxic drugs such as excessive doses of morphine, are to be corrected or avoided by proper measures.

Anesthesia for surgery of the liver should particularly meet three requirements in addition to those usually required of any good method. The method used must give good relaxation to permit upper abdominal surgery, it must not be toxic to the liver, and it must permit high oxygenation of the blood. Our choice of anesthesia, as well as that of others, is cyclopropane given by an intratracheal tube to assure adequate airway. This method also offers maximum relaxation with a high concentration of oxygen and minimal toxicity.

The incision of choice for the best exposure of liver tumors during resection, the most rapid healing, and least discomfort postoperatively appears to be either transverse or transrectus. Additional aids to exposure are hyperextension of the spine, severance of the ligamentous attachment of the liver and insertion of an inflated rubber glove to hold the liver down from the diaphragm. The liver incision should radiate out from the liver hilum to reduce the number of vessels and ducts severed.

Problems of resection of the liver are primarily those of hemostasis requiring a rapid method of control during the operation but one that is unlikely to result in secondary postoperative hemorrhage. Control of bleeding when a liver is involved by tumor is difficult for the following reasons: (a) the presence of tumor increases vascularity and hyperemia of the adjacent liver tissue; (b) the abnormal vessels supplying the tumor are less contractile, thinner walled and harder to ligate and are more susceptible to retrograde thrombosis with impairment of blood supply of the remaining liver; (c) the liver tissue adjacent to a tumor is friable and hard to suture; (d) the amount of functioning liver is reduced so that any injury, insignificant to a normal liver, may result in irrecoverable damage and necrosis manifest by the so-called "liver death syndrome" (Sutton). Sudden hemorrhage can be controlled temporarily by pressure on the aorta or by manual squeezing or clamping the vessels within the hepatoduodenal ligament. Clamps must be removed before 30 minutes have elapsed although manual squeezing is intermittent enough so that the vessels may be held longer. Autotransfusion with the blood in the abdomen can be done after citration and filtration through gauze if less than 24 hours old or after testing for agglutinins and hemolysis if over 24 hours old. Less severe hemorrhage may be controlled temporarily by: (a) digital compression of the cut edge of the liver; (b) tourniquet of the liver proximal to the bleeding edge; (c) tamponade of the bleeding surface; (d) application of spring clamps or rubber-shod intestinal clamps near the edge; or (e) controlling the oozing with adrenalin solution 1:1000 or 1:10,000, making the larger bleeding vessels discernible enough to be clamped and ligated (Hochenegg, Anschutz).

Methods of resection of tumors of the liver can be divided into eight major types with various additional modifications. The methods and the surgeons who first reported their use are: (1) elastic ligature compression of the stump usually with extraperitonealization by Cousins, 1874; (2) simple cautery removal by Escher, 1886; (3) lobectomy of the portion involved by tumor by Langenbuch, 1888; (4) suturing the liver for hemostasis before resection and closure of the cut end afterward by Kousnetzoff and Pensky, 1896; (5) placing of clamps that are left on the edge by Clementi, 1890; (6) tamponade by Anschutz, 1903; (7) cutting and hemostasis by electrocautery alone by McLean, 1929; and (8) the most recent and apparently most effective combination of first suturing for hemostasis and then excision by carefully controlled electrocautery (Fig. 2).

The combination of sutures for hemostasis preceding the electrocutting of the portion to be excised, as used by Dr. Reid of the Cincinnati General Hospital, appears to give better results than do other methods of resection. The hemostatic sutures control most of the bleeding so that a minimal coagulation of the surface is necessary, thus leaving the least possible eschar that must slough off before healing occurs. In addition to the hemostatic sutures, rubber-shod clamps may be used to control surface ooze and be released to reveal vessels that need ligation. In a wedge-shaped resection radiating out from the hilum there is minimal cutting of large vessels, and the longitudinal hemostatic sutures will support and prevent the cutting-in of the transverse sutures that approximate the two raw surfaces. Cautery resection without hemostatic sutures produces a thick eschar that requires drainage and prevents primary closure of the liver edge. In a recent case

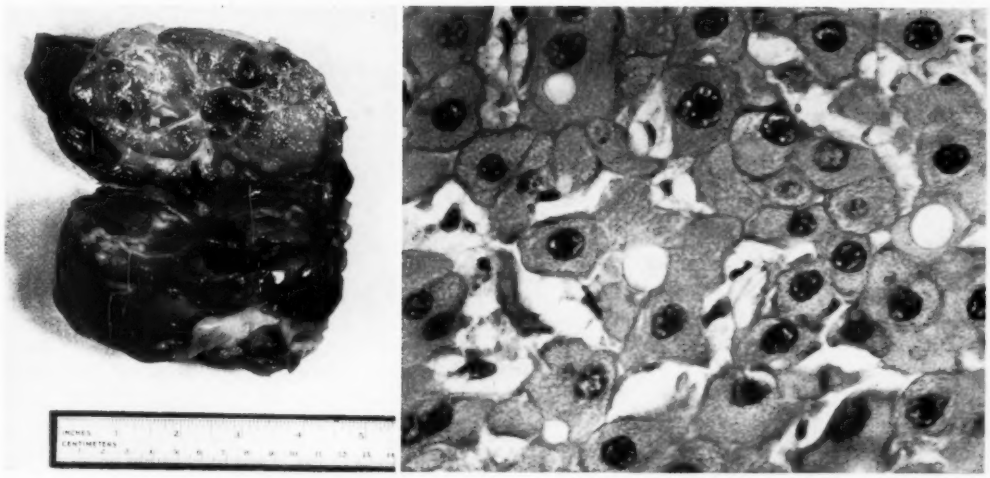

Fig. 1. Case 3. a, left, Resected adenoma cut open to show encapsulation. b, Adenoma of liver. Photomicrograph showing large cells in corded arrangement and uniform nuclei.

of adenoma in which cautery was the only means of hemostasis discharge continued 2½ months.

A comparison of adenoma cases resected with cautery with and without preceding hemostatic sutures illustrates the value of control of bleeding by sutures preventing dangerous blood loss and permitting more careful resection. Of 8 resected with cautery alone, 4 showed excessive bleeding during operation and 3 developed fatal bleeding within 6 hours, while of 11 cases resected with hemostatic sutures plus cautery, only 1 showed excessive bleeding during operation, and there were no deaths from hemorrhage.

X-ray therapy has been found to be of little or no value in the treatment of liver tumors. Only a few reports (Tinker and Tinker) claim response in liver tumors to x-ray. Jackson advises its use only as a placebo for the benefit of the relatives of a patient with an inoperable lesion. Harmful effects, rather than curative, were observed at the Cincinnati General Hospital, and the majority of reports in literature concur with this opinion. Reports include severe systemic reactions (Pohle), suppurative cholangitis and multiple liver abscesses (Pack and Livingston), and increasing anemia (McRae). Hence, x-ray therapy appears to be not only useless but also contraindicated for liver tumors.

CASES OF ADENOMA OF LIVER CELLS RESECTED AT THE CINCINNATI GENERAL HOSPITAL

Case 1. No. Q11045, F. A., admitted to hospital, September 23, 1931, white male, aged 45 years, who had noted a lump below the right costal margin for 1 year before admission. It had increased in size gradually and caused some dull pain. He had no jaundice or gastrointestinal disturbances. Examination was negative except for the mass attached to the liver, moving with respirations, firm and nontender. Clinical diagnosis was liver mass, type unknown. X-ray studies localized the mass as part of the liver displacing the other viscera. Intravenous pyelograms showed the kidneys to be normal.

Operation was carried out October 3, 1931, by Dr. B. N. Carter. Spinal anesthesia was used, supplemented by open drop ether as spinal wore off. Right rectus incision was used. Omentum was adherent to a firm nodular tumor 9 by 9 centimeters attached to the lower surface of the right lobe of the liver. Two large mattress sutures of chromic catgut were placed for hemostasis at the deepest portion beyond the tumor and the mass was excised distally. However, the tumor extended deep toward the hilum and did not appear to be completely removed. The omentum was attached over the line of resection and 2 cigarette drains were placed down to it. Silver wire stay sutures were used to re-enforce the closure of the abdomen.

Pathologic examination revealed the tumor to be a typical adenoma of the liver cells completely encapsulated except at the deepest portion where it appeared incompletely removed. The surrounding liver was normal except for some round cell infiltration.

The postoperative course was uneventful. X-ray therapy was attempted but was discontinued because of severe nausea and vomiting. He gained 30 pounds in weight and felt well until 3 years later when the mass recurred in the right upper quadrant, associated with jaundice and clay-colored stools. X-ray therapy to a total of 3500 r and skin dose 200 kilovolts with 2 millimeters aluminum and 0.5 millimeter copper filtration was given at irregular intervals because of nausea and vomiting with no improvement or reduction in the tumor. He died at home with symptoms and signs of portal and biliary obstruction 3 years and 5 months after operation.

Case 2. H. H. No. 340661, V. S., a white female, aged 42 years, whose illness began May, 1934, 6 months before ad-

mission to the hospital, when she noted a dull pain in the right upper abdomen that extended posteriorly to the inferior angle of the scapula where it was most marked. At the same time she noted a mass in the right upper abdomen that remained unchanged. She felt distended after meals with occasional nausea. There had been no vomiting, jaundice, nor loss of weight. Examination was negative except for the 8 centimeter mass attached to the liver, assumed to be of gall-bladder origin.

Operation was performed on November 28, 1934, by Dr. Mont R. Reid. Ether-oxygen anesthesia was used. Through a right rectus incision an 8 centimeter mass was revealed, covered by adherent omentum and attached to the right lobe of the liver by a 5 centimeter base near the fundus of the gall bladder. The cystic duct was divided and the gall bladder freed to a point near the tumor. Two rubber-shod clamps were placed across the liver, radiating from the hilum proximal to the tumor and (64) interrupted mattress sutures of chromic catgut were placed for hemostasis longitudinally proximal to the clamps. The tumor was then excised with electrocautery and the clamps removed. The cut edges were sutured together with No. 2 chromic catgut suture supported by the longitudinal hemostatic sutures. A cigarette drain was placed down to the stump of the cystic duct and the incision closed.

Postoperatively there was considerable abdominal distention for 3 days, relieved by enemas and pitressin. The drain was removed on the 4th postoperative day and she was discharged from the hospital on the 19th day in very good condition. She has been seen repeatedly at frequent intervals and has remained in good health over 8½ years, with no signs and symptoms.

Microscopically the tumor was a typical adenoma of liver cells completely encapsulated.

CASE 3. C. G. H., No. 161538, A. D., this patient, a 38 year old negro, began to have pain in the middle of the back July, 1940, 17 months before admission to this hospital. In October, 1940, he noted a golf ball sized, slightly tender epigastric mass that moved with change of position of the body. He went to several physicians and was given medication without improvement. He was worried and lost 20 pounds in 6 months. An exploratory laparotomy and a biopsy of the mass was done March, 1941, at another hospital. He was told that he had an inoperable carcinoma of the liver. He continued to lose weight while seeking treatment elsewhere and entered this hospital November, 1941. Our review of the microscopic slide ot the biopsy led to a diagnosis of an adenoma of liver cells.

Operation was performed November 15, 1941, by Dr. B. N. Carter. It was done through a transverse incision that crossed the right rectus scar of the previous operation and a T-extension was made along the old scar for better exposure. Adhesions had formed between the old scar and tumor to the anterior abdominal wall and the transverse colon and omentum. The structures were freed and the liver tissue compressed by the fingers of the assistant while the tumor was progressively resected with a Bovie unit and suture across the line of incision with No. 2 chromic catgut was carried out as the resection progressed. Six cigarette drains were placed down to the charred edge of the liver and the closure of the abdominal wall was re-enforced with silver wire stay sutures. Postoperatively he developed a bronchopneumonia, which responded well to sulfathiazole therapy. The thick discharge from the eschar obstructed the drains so that on the 17th day his temperature again rose to 101.6 degrees. Round rubber drains replaced the cigarette drains and proved to be adequate but he continued to have persistent discharge from the wound for over 12 weeks until the sinus finally closed. Since that time he regained his weight and has been in good health without signs of recurrence now for over 29 months since the resection of his tumor.

The tumor measured 13 by 9 centimeters and was completely encapsulated. Microscopically it was a typical adenoma of liver cells (Fig. 1, b).

A review of all reported resections of liver tumors totals 223 cases with complete description of operations as well as microscopic confirmation of diagnoses. Notable reviews of the past include those of Keen, 1892, 1897, and 1899; Anschutz, 1903; Cullen, 1905; Schroeder, 1906; Garre, 1907; McDill, 1912; Thole, 1913; Yoeman, 1915; Tinker, 1935; and Charache, 1939. Since the number of resections performed by any one surgeon are very few, a review of all reported cases offers the only way of adequate comparison of the various methods of resection.

There remain 347 resected cases that could not be included in tabulating and evaluating treatment because the referring authors did not give the source of the report mentioned, because some references were incorrect, some were in unobtainable journals, and a large number did not give adequate information about the case or the diagnosis was questionable. These include 273 resected cases of primary carcinoma of liver cells, 34 resected cases of primary sarcoma of the liver, 26 resected cases of solid adenomas of the liver, 8 resected cases of gall-bladder carcinoma invading the liver, and 6 or more resected cases of cystadenomas of intrahepatic bile duct origin. If all these cases could be accepted, there would be a total of 570 resected cases of liver tumors.

There are 6 common postoperative complications for which the surgeon must be on the alert: (1) Blood loss is no longer as much a danger as it was, for in Keen's review (1899) of 74 cases there were 11 deaths, of which 8 or 73 per cent were due to hemorrhage. Since the beginning of this century in 149 cases resected, there were possible manifestations of bleeding with fatality in only 3 cases (Mantle, 1903; Parin, 1913; Ramsey, 1929) and of these only 1, a hemangioma, had gross hemorrhage. (2) Infected wounds, peritonitis and septicemia are also much less important than in the past. (3) Prevention and chemotherapy have minimized the importance of respiratory complications such as pneumonia and atelectasis. (4) Three forms of metabolic disturbances giving rise to postoperative difficulties are: (a) "liver shock" (Ravdin) or "liver deaths" (Sutton) which occurs earliest, (b) "hepatorenal syndrome" and (c) general malnutrition largely as hepatic hypoglycemia which occurs late. (5) Postoperative ileus and at times hematemesis follow clamping of hepatoduodenal vessels with engorgement of portal cir-

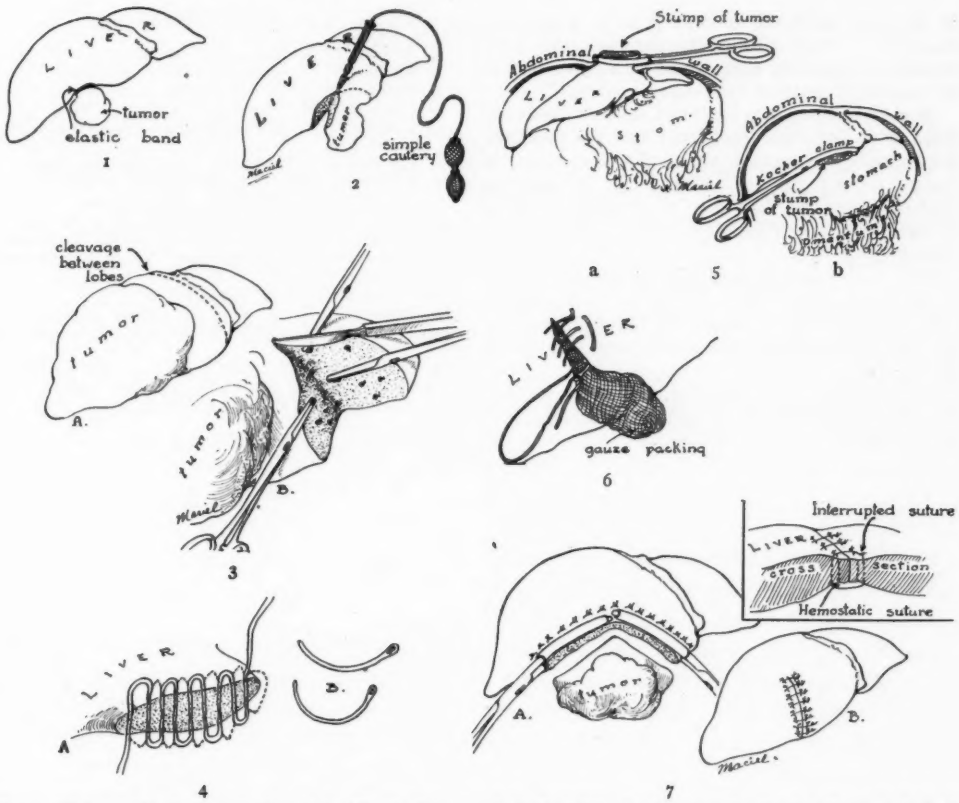

Fig. 2. Major methods of resection: (1) Elastic ligature and extraperitonealization of the stump (Cousins, 1874). (2) Simple cautery (Paquelin) removal (Escher, 1886). (3) Lobectomy with reported less bleeding for physiologic line of cleavage used (Langenbuch, 1888). (4) Hemostatic suture with blunt needle and closure of liver surfaces after resection (Kousnetzoff and Pensky). (5) Clamps left on for hemostasis and, a, completely exteriorized (Lapoint, 1897) or b, only the handles exteriorized for removal through a stab wound (Kocher, 1902). (6) Excision with tamponade (Anschutz, 1903). (7) Hemostatic sutures placed proximal to clamps and electrocautery excision of tumor distal to clamps. Raw surface closed by interrupted sutures going around the longitudinal hemostatic sutures preventing cutting of sutures through liver tissue. This method was used in Case 2.

culation. (6) Persistent sinuses occur with discharge of bile after marsupialization of cystadenomas, with discharge of necrotic slough from an excessively thick eschar of cautery or with discharge of pus from tracts left by drains.

SUMMARY AND CONCLUSIONS

A practical classification of primary tumors of the liver is presented with definition of terms. Emphasis is placed on the pathologic differentiation of true adenomas that are resectable with a good prognosis.

Clinical diagnostic features stress the local manifestations of benign tumors in contrast to the systemic disturbances of malignant tumors particularly those that are inoperable. Bile duct carcinoma tends to be more rapidly fatal and anaplastic than those of liver cell origin.

Diagnostic error clinically was less than 30 per cent. A table of differential diagnosis between benign tumors, primary carcinoma, and secondary malignant tumors is given.

Treatment of liver tumors must be entirely surgical to be successful. X-ray therapy is not only ineffective but detrimental. Surgical resection should be attempted in all localized liver tumors without evidence of involvement of adjacent organs or too much of the liver itself and should

be deferred until the patient is in best possible condition. After proper preparation the best method of resection appears to be a combination of hemostatic sutures and electrocautery.

Review of literature indicates that 223 resected cases have been fully reported but the probable total number of cases is about 570 when those of limited description are included. It is apparent that the operative mortality is not high but most failures are due to inadequate removal with recurrence.

Postoperative complications are largely those of metabolic disturbances such as early "liver deaths", late "hepatorenal syndrome," or finally malnutrition with loss of resistance to infection. These are preventable.

In conclusion, an attitude of futility should not be entertained toward all patients with primary liver tumors.

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THE CLINICAL USE OF BORIC ACID

OUR medical journals and daily newspapers announce with grim regularity the tragedy of death from boric acid poisoning in hospitals and clinics all over the country. And it is obvious that the reported cases, though seemingly numerous, do not constitute the aggregate of victims suffering this tragedy. Evidence that the problem has exceeded the academic stage of discussion is indicated by the fact that the toxicity of this compound was brought up for discussion at the recent National Chemical Exposition; and one state legislature already has up for consideration a statute to outlaw its unprescribed use.

The poisonous nature of boric acid was recognized as early as 1883, when Brose reported a death following its use as a dusting powder on a chronic leg ulcer. Subsequent reports have demonstrated its toxicity when absorbed from the gastrointestinal tract or when administered parenterally, and poisoning has been described in infants who have suckled from nipples cleansed with saturated boric acid solution. There have been reported numerous deaths due to the absorption of the drug from cavities, such as the pleura, that have been irrigated with solutions of boric acid, in the treatment of infections. Recent investigations by the Naval Medical Research Institute have demonstrated that boric acid, whether applied in the form of a saturated solution or as an ointment, is absorbed from extensive wounds or burns and is a cumulative poison.

Investigation into the mode of administration in fatal cases discloses that in some instances poisoning occurs when the physician who prescribes it does not know of the harmful nature of the drug, while in other instances the toxic substance is unintentionally substituted for an innocuous solution. Typical accidents that have occurred repeatedly are: the intravenous administration of boric acid solution in the place of glucose or saline solution which had been prescribed; and the preparation of infant feeding formulae with boric solution instead of sterile water. The frequency of such unwitting and accidental poisoning suggests that the universal employment of boric acid today constitutes one of those habits acquired by inheritance—and never critically evaluated.

The medical profession has used boric acid since Joseph Lister in 1875 in his communication, entitled "On Recent Improvements in the Details of Antiseptic Surgery," first described its use in clinical medicine. Lord Lister had employed it himself first in the treatment of an onychia on his little finger. He observed that a dressing saturated with

boric acid was more soothing to his finger than one with carbolic solution, and that the infection subsided promptly after its application. He concluded: "Here, then, I had at once sufficient evidence that the new antiseptic, when employed in the form of a watery solution, was both highly efficient and much less irritating than carbolic acid." The general acceptance of this "innocuous, odorless, and practically tasteless" substance was no doubt enhanced when its mildness was compared to the robust character of the antiseptics that were the order of the day. Boric acid was soon widely used for the dressing of wounds and for the irrigation of inflamed cavities.

The widespread use of boric acid solution today probably derives chiefly from the inertia of established custom; and its clinical survival no doubt results more from its property of blandness than from any of its other attributes, for it is not a satisfactory antiseptic. On the basis of our present knowledge of its toxic properties boric acid should be regarded by the medical profession as a poison and should be handled as such.

REED M. NESBIT

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE third edition of *Interns Handbook*[1] is a small volume planned to fit the coat pocket of its owner, yet supposed to contain a complete summary of medical and surgical therapeutics. Its opening pages deal briefly with instructions for the interne concerning his duties and responsibilities in hospital life. This is followed by a section on medical laboratory techniques. The third and fourth parts are given over to medical and surgical procedures, while the last section concerns itself with a description of numerous drugs and biologicals.

In general the aim at completeness in scope has resulted in an unbalanced spread of details. An attempt has been made to cover all disease entities with no heightened emphasis upon situations which commonly arise. The chief example of its sparseness of detail is the section on surgery where only general outlines are given, while the rarest of medical situations appear to be very well anticipated. While brevity is the byword throughout, the sections on laboratory techniques and pharmacology have used space which otherwise could have been devoted to clinical procedures whose details often are hidden in the literature, yet are well known to more experienced practicing physicians. There is no doubt but that the text has merit because it is such a compilation, but one feels that it will be more satisfactory to a senior medical student just starting his hospital experience than to an interne who is about to accept a greater degree of responsibility.

This text cannot supplant the average hospital procedure book, but in the absence of the latter it will be an aid to the unguided interne who feels the need of readily available pocket information.

WALTER W. CARROLL.

IN the fourth edition of the former *Manipulative Surgery*[2] many additions and alterations have been made, and some sections have been largely rewritten. A number of new illustrations of manipulative technique have been added.

Misapprehension frequently exists among the profession as to what manipulative treatment means and what it can achieve. There is also a tendency to emphasize unduly the dangers of manipulation. This book shows exactly what treatment by manipulation means and that intelligent discrimination is as necessary in this as in any other branch of surgery.

This subject is not sufficiently emphasized in the curricula of our medical schools. Cures by manipulation are so many and so well authenticated that the subject demands the fullest investigation. The subject should be taught by lectures upon the underlying pathology and by actual practical demonstration in our medical schools and hospitals. Interest and enthusiasms must be aroused. Research must be conducted into underlying physiological and pathological principles; careful records must be kept. These procedures should be easy, for every out-patient department contains cases which urgently need manipulation.

This book points the way to accomplish good results by manipulation. Surgeons should read this book to see what the author, an orthopedic surgeon, believes treatment by manipulation will accomplish.

JOHN S. COULTER.

SOME investigators have recognized a relationship between immunochemistry and enzyme chemistry, yet physiological chemists in general have paid little attention to immunity and conversely immunologists have had small interest in the chemistry of enzyme action. *Immuno-Catalysis*[3] by M. G. Sevag is an able elucidation of the author's theory of immunocatalysis. He demonstrates by an extensive and wise use of the literature the many parallelisms between protein antigen and enzymes and between antibodies and antienzymes, and by integration that antigens show properties which satisfy the well known criteria of catalytic agents and that specific antibodies formed as final reaction products in response to antigenic stimuli fulfill the function of specific inhibitors of enzymes. The book will especially interest immunologists and biochemists and act as a challenging incentive to further research. It is an excellent review of the literature with an exceptional bibliography. A. A. DAY.

BECAUSE of the outstanding qualities of the authors and widespread acceptance of their leadership in this field, it may seem unnecessary to review the book *Essentials of Oral Surgery* by Blair, Ivy, and Brown,[4] who, in long association, have been authoritative teachers of surgery and diseases of the oral cavity.

The arrangement of the material in the book conforms to that of Blair's original text *Surgery and*

[1] INTERNS HANDBOOK. By members of the Faculty of the College of Medicine, Syracuse University. Under the direction of M. S. Dooley, A.B., M.D., and Maynard E. Holmes, M.D., F.A.C.P. 3d ed. Philadelphia, London, and Montreal: J. P. Lippincott Co., 1944.

[2] TREATMENT BY MANIPULATION IN GENERAL AND CONSULTING PRACTICE. By A. G. Timbrell Fisher, M.C., M.B., Ch.B., F.R.C.S. (Eng.). New York: Paul B. Hoeber, Inc., 1944.

[3] IMMUNO-CATALYSIS. By M. G. Sevag, Ph.D. Springfield, Illinois, and Baltimore, Maryland: Charles C. Thomas, 1945.

[4] ESSENTIALS OF ORAL SURGERY. By Vilray Papin Blair, A.M., M.D. F.A.C.S., and Robert Henry Ivy, M.D., D.D.S., F.A.C.S., with the collaboration of James Barrett Brown, M.D., F.A.C.S. 3d ed. St. Louis: The C. V. Mosby Co., 1944.

Diseases of the Mouth and Jaws published in 1912, and much of this material has been retained. The new book, with the collaboration of the present authors, has been brought progressively up to date to the present third edition.

Primarily intended as a text and guide in surgery for dental students, the book maintains that objective and further provides a valuable source of information for medical students and practitioners on a subject rather neglected in medical education. The scope of the book is tremendous and most revealing to one not particularly familiar with the diseases and affections to be found in the oral cavity.

Particular importance is attached to the need for recognition of surgical conditions and, while the opening chapter deals exclusively with examination, anatomical considerations, and study leading to diagnosis, this emphasis is stressed throughout the book. This sound approach to the subject is founded on the unusual combination of abilities of these individual authors as teachers, clinicians, and resourceful surgeons. In this book the dentist will find the solution to his most disturbing problems—those concerned with acute and chronic infections and inflammatory conditions arising about the teeth, fractures of the jaws, dislocation of the jaw, and the loss of teeth or roots in the antrum.

The chapter written by Dr. Kazanjian on the surgical preparation of the mouth for artificial dentures will be particularly appreciated by the dentist who is anxious to improve the efficiency of his prosthetic efforts.

With the exception of the chapter on fractures of the jaws, that dealing with tumors is given most space (68 pages). This is one of the most important chapters in the book and the emphasis laid on precancerous lesions and cancer of the mouth and jaw bones is desirable and commendable.

The rôle of the dentist in the control of cancer is definite, and the plea is made for fundamental knowledge of oral pathology and a routine and complete survey of the whole mouth.

New material has been included to bring the sections on shock, hemorrhage, burns, and wounds up-to-date. Developments in the treatment of fractures are described and illustrated.

This book of 624 pages, with 467 uniformly good illustrations, is a desirable textbook for dental students and medical students, and deserves a place in the library of every surgeon and dentist.

FREDERICK W. MERRIFIELD.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

FISIOLOGIA ENDOCRINA. By Amado Ruiz Sánchez. Vol. 2. Guadalajara, México: Universidad de Guadalajara, 1944.

CLINICAL ROENTGENOLOGY OF THE DIGESTIVE TRACT. By Maurice Feldman, M.D. 2d ed. Baltimore: The Williams & Wilkins Co., 1945.

PENICILLIN THERAPY; INCLUDING TYROTHRICIN AND OTHER ANTIBIOTIC THERAPY. By John A. Kilmer, M.S., M.D., Dr. P.H., Sc.D., LL.D., L.H.D., F.A.C.P. New York and London: D. Appleton-Century Co. Inc., 1945.

A SYMPOSIUM ON MAMMARY TUMORS IN MICE. Publication of the American Association for the Advancement of Science No. 22. By Members of the Staff of the National Cancer Institute, National Institute of Health, United States Public Health Service. Edited by Forest Ray Moulton. Washington, D.C.: American Association for the Advancement of Science, 1945.

THE FUNDAMENTALS OF ELECTROCARDIOGRAPHIC INTERPRETATION. By J. Bailey Carter, M.D., F.A.C.P. With a Foreword by Horatio Burt Williams. 2d ed. Springfield, Ill., Baltimore, Md.: Charles C. Thomas, 1945.

THE NEW-BORN INFANT; A MANUAL OF OBSTETRICAL PEDIATRICS. By Emerson L. Stone, M.D. 3d ed. Philadelphia: Lea & Febiger, 1945.

CLINICAL CYSTOSCOPY; A TREATISE ON CYSTOSCOPIC TECHNIC, DIAGNOSIS, PROCEDURES, AND TREATMENT. By Lowrain E. McCrea, M.D., F.A.C.S. Philadelphia: F. A. Davis Co., 1945.

DISEASES OF THE NERVOUS SYSTEM IN INFANCY, CHILDHOOD AND ADOLESCENCE. By Frank R. Ford, M.D. 2d ed. Springfield, Ill.: Charles C. Thomas, 1944.

AMERICAN COLLEGE OF SURGEONS

GRADUATE TRAINING IN SURGERY AND THE SURGICAL SPECIALTIES

CHARLES R. REYNOLDS, M.D., Major General, U.S. Army (Retired), Chicago, Illinois

THE Surgeon General of the United States Army has announced that of the wounded who live to reach Army hospitals, more than 90 per cent are being saved. This is not entirely due to chemotherapy and the use of penicillin and blood and blood substitutes but to a large extent is the result of sound surgical principles applied to trauma. The surgical profession may well be proud of that accomplishment. Looking back over the road it has come, the profession knows that the surgical proficiency of today is the fruit of the decisive planning of yesterday through which the more or less haphazard apprenticeship system of training has been rapidly supplanted by scientifically set up, well rounded programs of graduate training in surgery.

Right now, when scientific surgery is being put to its supreme test, is the time for surgeons to resolve that the unavoidable disruption of surgical education by the war must be compensated for at the earliest possible moment. The temporary setback must be repaired by postwar plans so complete and progressive that they will take up the wartime lag and reinstate surgery on its forward march.

Dr. Dallas B. Phemister, chairman of the Committee on Graduate Training in Surgery of the American College of Surgeons said in an article in the February 15, 1942, issue of SURGERY, GYNECOLOGY AND OBSTETRICS, "The needs of our military forces must be met and under the present world conditions some of our most desirable and ambitious plans may have to be changed." The prediction has come true. We have had to curtail training in surgery at a time when we urgently need more and better trained surgeons. A decreasing number of trainees have been permitted to carry their educational programs through to completion. As the months pass and the war lengthens the situation becomes increasingly grave.

Consultant in Graduate Training in Surgery, American College of Surgeons.

EFFECTS OF PRESENT WAR ON MEDICAL EDUCATION

Under the Army specialized training program and the Navy V 12 program medical education on the undergraduate level has, up to the present time, been maintained on a reasonably normal basis considering the disruption of facilities and hospital staffs. The accelerated program has made possible the graduation of 5,500 doctors every 9 months, or at the rate of 7,000 every 12 months. Of course, the majority of the war time graduates enter military service after a 9 months' internship. The induction of premedical students will result in a decrease in graduates, and by 1948 and 1949 in shortage of physicians, calculated on a prewar basis.

Under the 9—9—9 plan hospitals may retain for a 9 months' assistant residency one-third of the men who complete the 9 months' general interneship, and may keep for a further 9 month period one-half of those who complete an assistant residency. As Dr. Frank Lahey, chairman of the Directing Board of the Procurement and Assignment Service has said, "The 9—9—9 program is working fine but no one likes it." Inadequate training is given the young men and they are not qualified under it to go out and practice medicine of a standard that the medical profession has set. It is a makeshift and compromise system which is one of the sacrifices that it has been necessary to make to win the war. Its faults make it the more urgent that plans be set up for further training of these men when the war is over. The abbreviated or hurried curricula in medical schools, the depletion of school facilities and hospital staffs, and the abbreviated interneships and curtailment of training at the residency level, all conspire to set back medical education in this country not only during the war but for several years afterward.

Great credit should be given to medical schools and teaching hospitals which have carried a heavy load of undergraduate and graduate education with depleted staffs.

PROFESSIONAL EXPERIENCE WHILE IN MILITARY SERVICE

As in all recent wars great advances in medical science are being made in this one. These have become evident in preventive medicine, treatment of tropical diseases, in chemotherapy and the use of penicillin in medical and surgical conditions, the use of blood and blood substitutes, in traumatic surgery and the control of wound infections and the treatment of burns and in the broad field, let us call it reconstruction surgery, wherein are to be included orthopedic, vascular, neurological, and plastic surgery and physical medicine.

By reason of concentration in large hospitals the casualties of war are conveniently arranged for medical and surgical practice and research on a very broad scale. Where in peacetime are to be found hospitals of 5,000 to 10,000 beds set aside for the care of special diseases and injuries? It is safe to say that there are several Army hospitals which are now caring for more neurosurgical cases than all the civilian hospitals in the country combined. The same may be true, to a less extent, as to amputation, fracture, vascular, orthopedic, and other cases for physical rehabilitation.

Unfortunately the great or overall advantages accruing to medicine as a result of this war are not participated in by a large proportion of the younger medical officers. When many of these men balance experience gained in the war against the loss of several years of training and practice, particularly if their specialty is surgery, they will find themselves several years behind their programs of graduate training.

Senior medical officers naturally occupy the higher professional positions where they are privileged to preserve or advance their professional status. The junior officers, with exceptions, are assigned to troop duty or small medical units. This being the toughest war in history, the demand for the young and vigorous and the tables of organization which determine assignments naturally place a preponderance of young medical men with the combat forces. The recent medical graduates fall into this group. Those who planned or started a surgical career have certainly had their graduate training "impeded, delayed, interrupted or interfered with" as expressed in the subsection on education of the "G. I. Bill."

The scope of wartime medical and surgical practice in the Army, except in some of the general and large area hospitals, is lacking in several important features which are necessary in a well rounded program of graduate training in surgery and the surgical specialties.

This is not to imply that all young medical graduates who enter the Army and Navy say goodbye to their graduate training plans for the duration. Those who are fortunate enough to serve in general or large area hospitals find themselves associated with specialists of the highest caliber, drawn from medical schools, teaching hospitals and clinics. Clinical material, though not diversified to cover the entire field of surgical training, is available. It is known that most of these hospitals are making a point to carry on comprehensive training programs for younger medical officers and otherwise to meet the "essentials" as laid down by the American Medical Association and the "standards" of the American College of Surgeons.

However, surgery at the front is limited quite largely to emergency surgery in which many junior officers see only the early treatment and, except when serving with auxiliary surgical operating units, do not take part in the definitive operative procedures and the postoperative care and rehabilitation of war casualties.

The age of the patients is young, mostly males from 18 to 38, with the exception of officers. Consequently, the medical officer gains relatively little experience with the conditions prevalent in middle and old age groups, such as the degenerative or chronic diseases—conditions becoming year by year more prevalent and of increasing importance to surgeons. There is also scarcity of experience in care of women and children, many getting no experience in obstetrics, gynecology, and surgical conditions of children and adolescents. Their experience is extremely limited too regarding the chief causes of death—heart disease, cancer, and apoplexy.

Another factor detracting from the educational value of medical experience in this war is the likelihood of prolonged absence from laboratory and research projects and from experience with the newer medical and surgical procedures in hospital practice.

It will be from this group of 18,000 or more younger medical officers, that requests for graduate training in surgery of a comprehensive type will come. Among its other objectives, the American College of Surgeons recognizes an obligation to develop programs and facilities that will make it possible for future Fellows to meet the requirements for fellowship especially in relation to graduate training in general surgery and the surgical specialties. Professional experience gained in military service will be evaluated and credit given by the College and the boards of medical specialties.

PROGRESS OF GRADUATE TRAINING IN URGERY

At this point it might be well to trace the origin and development of the system of graduate training that is recognized today to constitute adequate preparation for surgery. Nearly 30 years ago at a meeting of the Southern Surgical Association, Dr. Thomas S. Cullen, of Baltimore, credited the American College of Surgeons with beginning remedial measures to control "unwarranted operating by inexperienced men." That the most progressive minds in the profession were already thinking in terms of the extended training which all of us consider essential now, is shown by the further remarks of Dr. Cullen, as follows:

"The medical student who after graduation decides to make surgery his life work should not take up his chosen specialty at once but should spend at least one year in a strictly medical service. A broad foundation in general medicine is absolutely essential. The following year can be most profitably spent in the pathological laboratory in making and cultivating the bacterial flora associated with them. After this he should become a surgical interne under a competent surgeon. His time will now be occupied in taking histories, assisting at operations, and in the aftercare of patients. He will also have ample opportunity for studying all tissues coming from the operating room. He thus has a complete picture of the patient's condition from the time of admission until his discharge, and from the laboratory findings has a clear idea as to the ultimate prognosis of the case. After he has assisted from one to two years, he is allowed to perform the simpler operations, and by the end of the second or third year he is competent to handle the more difficult cases. After a year or two as resident surgeon he is amply fitted to start out as a full-fledged surgeon, with the definite knowledge on the part of the hospital that he will be a credit to the school and to the institution from which he has come."

Dr. Cullen went on to say that a lack of knowledge of pathology "is the weakest point in American surgery today," and we agree with his conviction that "to practice surgery without an adequate knowledge of surgical pathology is like building upon the sand."

Again and again through the years we find individual surgeons voicing the hope that the training of surgeons be placed on a scientific plane. The American College of Surgeons began to give the subject continuous consideration from 1930 on. In 1933 Dr. William D. Haggard told members of a Hospital Standardization Conference sponsored by the College that the most satisfactory preparation for a surgical career was "a residency in surgery, after a general hospital service, in a university or other hospital for 2 to 5 years, combined with some teaching." In 1935, Dr. Edward W. Archibald, in his presidential address to the American Surgical Association, said in part:

"There has arisen in considerable numbers a certain type of surgeon which we all recognize and deplore. He is the natural product of those discoveries and inventions—anesthesia, asepsis, fine tools, and well equipped small hospitals—which have rendered the practice of surgery in its purely mechanical aspects, relatively safe. He is progressive, venturesome, and self-confident, and such qualities are perhaps those which have placed the best of American surgery in its present proud position. But in the particular type to which I refer, venturesomeness becomes foolhardiness, and self-confidence is uncontrolled by knowledge. To such a man the sum of acquired knowledge is comprised in the popular theories of the year just past. Theory is counted as fact, the hypothesis as a thing proved. A decision to operate is based upon a medical catchword, or a rule of thumb. Fingers replace brains, and handicraft outruns science. The result is that such a surgeon is apt to undertake operations which may be technically possible, but which are scientifically unjustified."

Important developments with respect to stimulation of interest in proper training were organization of the American College of Surgeons in 1913, and formation of the specialty boards. The first specialty board, the American Board of Ophthalmology, was incorporated on May 3, 1917, to examine candidates and to certify those who passed the examination. The American College of Surgeons provided office space and secretarial aid for the first two years of this Board's existence. Ophthalmology as a specialty in America began in 1855 when Elkanah Williams, of Cincinnati, introduced the ophthalmoscope to this country and became the first American physician to limit his practice exclusively to ophthalmology and otology. Independent departments of ophthalmology and otology were established beginning with Cincinnati in 1860, Bellevue in 1868, Rush in 1869, Northwestern in 1870, Harvard in 1871, and Pennsylvania in 1872. Despite this academic recognition, ophthalmology was treated like a step-child, S. Weir Mitchell declaring in 1891 that he could remember the day in Philadelphia when "older physicians refused to recognize socially a man who devoted himself to the eye alone."

In 1869 the Committee on Specialties of the American Medical Association resolved that "this Association recognizes specialties as proper and legitimate fields of practice," but admitted that there were objections to specialties because "they operate unfairly against the general practitioner in implying that he is incompetent to properly treat certain classes of diseases and narrowing his field of practice."

At any rate, specialization grew. In 1924 the board of otolaryngology was established, in 1930 the board of obstetrics and gynecology, in 1932 the board of dermatology and syphilology, and in 1933 the board of pediatrics. Three boards were established in 1934: orthopedic surgery, psychiatry and neurology, and radiology. The board of urology was established in 1935, the boards of pathology and of internal medicine in

1936, the boards of surgery and of plastic surgery in 1937, the board of anesthesiology in 1938, and the board of neurological surgery in 1940.

THE AMERICAN COLLEGE OF SURGEONS' PROGRAM

The American College of Surgeons appointed a committee in 1928 to study what the requirements should be for training in surgery. They contributed a great many ideas. Finally, in 1935, a committee under the chairmanship of Dr. Samuel Harvey, New Haven, professor of surgery, Yale University Medical School, brought in a report supplemented by related reports by the associate directors of the College, Dr. Bowman C. Crowell and Dr. Malcolm T. MacEachern. Out of this study came the present plan for the promotion of training in surgery. This was followed by surveys in 1937 and 1938 for the establishment of a Minimum Standard, now used in the promotion of the work of graduate training in surgery and reproduced in this article.

A list of hospitals of the United States and Canada approved for graduate training in surgery was published first in January, 1939. The "Approval Number" of the *Bulletin* of the College published in October, 1940, contained a list of 200 hospitals which met the Minimum Standard for graduate training in surgery and also a directory of the approved plans, including detailed descriptions of the provisions for basic science study, supervision, and the gaining of practical experience. The directory was the first presentation of selected graduate training programs that had ever been made available to the graduate in medicine as a guide in his plans for qualifying himself to practice surgery. It makes possible careful selection of the institution which offers the program best suited to the individual's needs and offers ready opportunity for comparison of programs of different institutions. The new edition of the directory which will shortly be issued will bring the most up-to-date information regarding the approved programs to medical officers looking forward to demobilization and resumption of training. Other information of this nature will be imparted by the College upon inquiry received direct or through the information bureau of the American Medical Association.

One of the chief aims of the College in this program is to increase the opportunities for acceptable training in the moderately sized communities as well as the large medical centers, which will result in the distribution of surgical skill better suited to population requirements.

Preparation for the practice of surgery or a surgical specialty is so long and complicated a process that careful planning is essential. It has been the experience of the American College of Surgeons in studying the qualifications of applicants for fellowship that a large proportion either fail to make suitable plans for training, or veer from the course after they have embarked upon what would have been a suitable program. Advice is constantly being given concerning reconstruction of plans that have not provided the proper background. Considerable time must be spent with each individual advising and helping him with his problems, and the outlook is that the need for this service will be vastly increased when demobilization begins. The problems of evaluating experience while in military service will be added to those of appraising the training received prior to entering the service.

It is expected that physicians who will desire training in surgery after the war will be of 5 general types. These are listed as follows in the "War Issue" of the *Bulletin* of the American College of Surgeons, June, 1944:[1]

"1. Physicians who planned to specialize in surgery but who were commissioned immediately following their interneship.

"2. Physicians whose residencies in surgery were interrupted by military service.

"3. Physicians who, under the 9–9–9 plan, were deferred, receiving one or two 9-month periods of graduate training, and who will therefore require additional months of training to complete 3 full years following a 12 months' interneship.

"4. Physicians who in military service have received some training in surgery which, supplemented by further training, would be recognized as acceptable preparation for the practice of surgery.

"5. Physicians with acceptable qualifications who had been in general practice prior to military service and who have gained a desire to specialize in surgery."

The American College of Surgeons, through its Department of Graduate Training in Surgery, is pledged to give every possible assistance to the returning medical officer who desires to complete his training so that he may achieve his aim of meeting the criteria of fitness in the specialty of his choice.

Sixty thousand of the approximately 135,000 physicians engaged in active practice in the United States are serving with the armed forces. At present, some 18,000 of these are recent medical graduates whose training has been interrupted. An analysis of about 21,000 returns from the questionnaires sent to 60,000 medical officers by the American Medical Association indicates that four-fifths want some kind of postwar training. Three-fifths indicate desire for long courses and one-fifth prefer short courses (less than 6

[1]MacEachern, Malcolm T., Bull. Am. Coll. Surg., 1944, 29: 2, 206.

MINIMUM STANDARD FOR GRADUATE TRAINING IN SURGERY

1. DURATION AND OBJECTIVE. Graduate training in general surgery and the surgical specialties shall be of sufficient duration and educational content to enable the young surgeon, upon completion of such training, to begin the practice of surgery in a scientific manner. An acceptable program requires a minimum of two and preferably three or more years.[1]

2. ORGANIZATION AND SUPERVISION. (a) The medical staff shall be organized with heads of departments and a representative committee responsible for the organization of the graduate training program and for the personal supervision and direction of the work of the resident staff. (b) The hospital shall keep such records of the activities of the resident staff as may be necessary to assure an equitable distribution of work, and together with some form of examination, provide a basis upon which the plan of graduate training may be evaluated.

3. BASIC MEDICAL SCIENCES. (a) The hospital shall maintain a clinical laboratory, an x-ray department, and other adjunct diagnostic and therapeutic facilities essential for diagnosis and treatment. Facilities for other basic science study, research and investigative work are desirable. (b) All services shall be under the continuous supervision of accredited heads of departments and have qualified technical assistants. (c) The resident staff shall be required to observe and participate in autopsies, to devote adequate time to the study of gross and microscopic pathology, to acquire a degree of practical knowledge of clinical roentgenology and radiology, to pursue anatomical studies by dissections on the cadaver and animals, to participate in clinical or experimental research; or to devote definite time to other study of the basic medical sciences.

If not available within the hospital, provision for adequate collateral study of the basic medical sciences shall be provided through affiliation with another hospital or educational institution.

4. CLINICAL MATERIAL. (a) The hospital shall have an active surgical service and an organized out-patient department with systematic follow-up clinics. (b) The number of patients shall be adequate to give the resident staff opportunity for training and experience in the diagnosis, treatment, and study of end results of a variety of surgical conditions. (c) Operative experience, under supervision, sufficient to obtain a degree of technical efficiency shall be provided for the resident staff.

5. ORGANIZED STUDY. (a) The hospital shall provide a medical library containing a wide range of standard textbooks, current medical journals and periodicals, with a librarian in charge. (b) A definite program of reading of scientific literature under guidance of the medical staff shall be required, and the resident staff shall take an active part in general staff conferences, departmental conferences, clinicopathological conferences, and be responsible for some teaching activity.

[1]Since the Minimum Standard was adopted, the Committee on Graduate Training in Surgery has agreed that the duration of an acceptable program should be three or more years following interneship; this change in Clause I awaits the official consideration of the Board of Regents.

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months). Applying these factors to the total of 60,000 it will appear that 48,000 medical officers now in service will look for postwar training.

The following are extracts from the report of the replies sent to medical officers in the armed services as compiled by Lieutenant Colonel Harold C. Lueth, M.C., Surgeon General's Office, Liaison Officer, American Medical Association.[1]

"Requests for short courses included all specialties. The largest number of requests were for the following specialties in order of frequency: internal medicine, surgery, general review, obstetrics and gynecology, pediatrics, otolaryngology and ophthalmology.

"The 10 most popular special fields of training by means of long courses, in order of frequency of request, were surgery, internal medicine, obstetrics and gynecology, general review, psychiatry and neurology, pediatrics, orthopedic surgery, ophthalmology, radiology, and otolaryngology.

"Nearly two-thirds of the group, 13,333 or 63 per cent, expressed a desire to become certified specialists. There were 3,324 medical officers, nearly 16 per cent of the entire group, already certified by the American specialty boards. The remainder either did not care to be certified or did not mention their desires.

"Nearly 40 per cent, 8,734 medical officers, came from private practice to the military services. Twenty-two per cent, 4,640, came directly from interneships; nearly 10 per cent, 2,191, came directly from residencies, and the remainder came from various types of practice. About 15 per cent failed to answer the question concerning their previous type of medical practice.

"A comparison of the results of a pilot questionnaire and the present questionnaire was made. Long courses were requested by about one-fifth more in the final questionnaire than in the pilot questionnaire. Only two-thirds as many men requested short courses in the final questionnaire as in the pilot. The difference was attributed to a change of viewpoint of medical officers during the interval between the circulation of the questionnaires rather than to an error in sampling."

Very significant in this report is the number of medical officers who entered military service directly from interneships—22 per cent—and 10 per cent additional directly from residencies.

The importance of training for demobilized physicians is well expressed in the interim report to the Senate Committee on Education and Labor from the Subcommittee on Wartime Health and Education dated January 2, 1945, quotation from which follows:

[1]J. Am. M. Ass., 1945, 127: 658.

"... the accelerated undergraduate courses, and the shortened interneships and residencies, will make it necessary to provide further supervised training for many recent graduates unless the future quality of medical and dental practice is to be jeopardized. Most of the young graduates are well aware of this.... Neither the need nor the demand for postwar advanced medical training can be met with the graduate teaching facilities and staffs now available in medical schools. Expansion of such facilities through increased provision of teaching hospitals and medical centers, as part of the program hereinafter described and recommended, will therefore be required."

As new medical graduates go into service after the abbreviated 9 months' interneship, and as current graduates, postwar, swell the numbers of those wanting and needing surgical training, it becomes obvious that hospitals will be swamped with demands for training appointments when demobilization begins. It is fair to assume that at least 15,000 medical officers now in service will require some kind of surgical training, at least 10,000 of whom will require extended training in surgery and the surgical specialties. There will be at least double the number of applicants for training than could be accommodated in the 231 hospitals which after survey and careful study of the findings have been approved by the American College of Surgeons for graduate training in surgery and the surgical specialties. Those hospitals are organized at present to train about 1,234 surgeons, with a possible expansion in the crisis to 1,900. Among these are the hospitals connected with medical schools which have been carrying the major load in graduate education, and have been getting excellent results. They cannot accept much more responsibility. Their contribution must be supplemented by the educational efforts of non-university connected hospitals. Therefore about 250 additional hospitals must be assisted in creating a total of approximately 3,000 residencies in surgery to be ready to meet the expected requirements of those now with the armed forces. This places the problem squarely before us of surveying a total of at least 500 hospitals. The rate of release from military service, though not yet known, is quite certain to result in a substantial demand soon after the cessation of hostilities in either major theater.

To further the program the Department of Graduate Training in Surgery has been expanded. On October 1, 1944, Dr. George H. Miller, formerly dean of medicine, American University of Beirut, Lebanon, Syria, joined the staff as director of educational activities. At the same time, the writer was appointed consultant in graduate training in surgery. Dr. Paul S. Ferguson, who has been on the College staff for a number of years and has been in charge of surveys for graduate training in surgery, was appointed director of surveys. The field staff for survey work will be enlarged to include at least 4 competent assistants. In addition, the field men making the regular Hospital Standardization surveys under the direction of Dr. E. W. Williamson, assistant director of the College, assist with the work in graduate training in surgery. The associate directors, Dr. Malcolm T. MacEachern and Dr. Bowman C. Crowell, are very active in the work.

In undertaking this program the College has had rich experience over a period of 27 years in its Hospital Standardization program and has obtained valuable data upon which to base its program for graduate training in surgery. It has on file about 60,000 reports of hospital surveys.

Although general principles governing educational content of the training plans have been laid down in the Minimum Standard which accompanies this article, no set pattern can be developed because of the wide variations between the institutions which can furnish acceptable training. After certain fundamental requirements are met, there is room for considerable latitude in the details of operation. The essentials are concerned with duration, which must be not less than 3 years following interneship; organization and supervision, which implies a well organized medical staff including exclusive specialists in their respective fields who possess teaching ability, and who are given definite teaching responsibilities including supervisory duties and the selection and examination of graduate students; ample provision of facilities for and supervision of basic science study; an active surgical service, an organized outpatient department, and sufficient patients to provide ample clinical material and operative experience, under supervision, for the resident staff; and provisions for organized study through a medical library and a definite program of reading and scientific reviews, in addition to participation in general staff, departmental and clinicopathological conferences, and opportunities for some teaching activity on the part of residents.

Within this framework there is room for individualization according to the type of institution, whether it be the large hospital directly connected with a medical school, the small hospital which arranges affiliations with other hospitals for broader clinical experience and with a medical school for basic science study, or the clinic which adds to its well set-up apprenticeship type of training closely supervised by thoroughly qualified surgeons the benefit of facilities for study of the basic medical sciences and research.

The greatest obstacle to most hospitals in setting up graduate training in surgery programs is an arrangement for study of the basic medical sciences. It is difficult to lay down a definite program for graduate training in the basic sciences as there still exists a difference of opinion as to just what constitute the basic sciences in relation to surgical training, or, at least, to what extent and when these should enter into the graduate program. Authorities, however, seem to agree that they include anatomy, physiology, biochemistry, pathology, bacteriology, and roentgenology, and that at the graduate level they should be taught by the applicatory system so far as possible. Some believe that they should be taught over a period up to 12 months at the beginning of the training program, or in a subsequent year, whereas others believe this training can be obtained throughout the several years of residency in hospitals well organized for educational purposes. The latter lean especially to the idea of the resident obtaining this training through special research projects so far as practicable. Perhaps the concensus is that so far as pathology and roentgenology are concerned, hospitals which have competent pathologists and radiologists on their staffs may be able to arrange teaching programs right in the hospital throughout the residency. The same is true of biochemistry and bacteriology which can usually be taught by practical experience in the laboratories. For the teaching of anatomy and physiology, on the other hand, definite medical school affiliations are most desirable, although there will be cases of hospitals which can furnish excellent resources for study even in these subjects. In general, however, hospitals cannot provide opportunities for cadaver dissection due either to lack of facilities or to legal restrictions.

In approving hospitals for graduate training, full consideration is given to all of the factors involved in a given situation, with proper credit for resourcefulness in devising ways of giving the students adequate training—there is no set pattern that will govern all cases, and no intention to handicap certain hospitals by adhering to a rigid, specific plan that they cannot possibly meet.

Studies now being made by Dr. George H. Miller of the College staff, by personal visits to selected medical centers in the United States and Canada to study existing plans and further possibilities for co-ordination of graduate training between hospitals and medical schools, will throw much light on the means of solving the problem of the basic medical sciences, an up-to-date knowledge of which will be especially valuable to those returning from military service. Under all circumstances it is essential for a man preparing to become a competent surgeon to know the fundamental sciences. To ignore the applied sciences in the scheme of training would lower the standards of surgical practice.

The picture before us is the medical veteran returning home after making a substantial and costly contribution to his country's security. He is asking, and will expect, to re-establish himself in the study or practice of surgery in the most approved, scientific way. From the standpoint of patriotism alone that obligation on our part is a compelling one. If this situation is not met substantially as the College proposes to meet it, the result will be distressing disillusionment, occasioned by many young medical men having to go into practice without completing their plans for special training, and a serious setback to the standards of surgical practice so substantially advanced in this hemisphere in recent years.

Another consideration is that medical education has been practically suspended in many of the countries of Europe and Asia. For years to come the United States and Canada will be looked upon as centers for postgraduate medical education to meet the requirements of students in war-torn countries as well as those from South and Central America who, even before the war, had begun to seek training opportunities in North America.

THE G. I. BILL

The financial problems of the demobilized physician who wishes to resume his training will be somewhat simplified by the Service Men's Readjustment Act, popularly known as the G. I. Bill, which was approved on June 22, 1944. Under this Act a veteran while enrolled in and pursuing a course of education or training in an educational institution which term includes teaching hospitals, may be paid a maintenance allowance of $50 per month if without a dependent, or $75 per month if he have a dependent or dependents. Medical schools and hospitals may also receive up to $500 a year to cover cost of tuition, laboratory fees, books, supplies and equipment exclusive of any charge for maintenance for each student who is accepted for training under the G. I. Bill. To be eligible for educational benefits the discharged veteran must have been in active service not less than 6 months, or shall have been discharged or released from active service by reason of an actual service-incurred injury or disability.

GRADUATE TRAINING IN GOVERNMENT HOSPITALS

The College has surveyed 31 United States Naval Hospitals, 9 United States Public Health

Service hospitals, and 20 Veterans Administration hospitals, to determine their qualifications for graduate training in surgery. It seems impracticable to establish comprehensive programs of training in Army hospitals under existing military conditions, but such training may be considered as a postwar program. However, short courses of training "on the job" for volunteers are now being carried on in selected hospitals, chiefly for the benefit of medical officers who have been on administrative duty or in combat areas where opportunity for professional service has been lacking. Plans are now under way to establish graduate training programs substantially as formulated by the American College of Surgeons extending over a period of 4 years, less credit for worthwhile experience, in a number of hospitals of the Navy, the United States Public Health Service and the Veterans Administration. What has been said before regarding the clinical material in service hospitals available for surgical training should be borne in mind in estimating this feature of the program of the College.

It is likely that long or comprehensive programs of training will be established when the military situation clears. Such programs will be an inspiration to officers to carry out their purpose to become proficient in surgery and to meet the requirements for fellowship in the College and for certification by the specialty boards. Officers, while receiving this training, will be on active duty with pay and emoluments, and they will have the benefit of almost constant association with the chiefs of services on full time duty in the hospitals. Such a program of training will facilitate expansion and reorganization of the Army, Navy, and Veterans Administration by attracting temporary officers who are interested primarily in a surgical career.

If history is repeated the Presidential proclamation terminating the national emergency may be delayed as long as two years after the cessation of active military operations which, with the "six months thereafter" as provided by existing law, will offer an excellent opportunity for graduate training in the service hospitals over a considerable period of time and will correspondingly ease the training load to be carried by civilian hospitals.

THE PUBLIC INTEREST—MEDICINE'S OPPORTUNITY

The prospects are that the postwar period will bring unprecedented demands for the services of surgical specialists. The first World War gave tremendous impetus to medical and surgical specialization. Today war medicine is again contributing to enhanced appreciation of the value of the surgeon who has exceptional skill in a specific field. Aroused public interest is medicine's opportunity.

Special skills are best developed through systematic educational programs, in selected hospitals, whereby the fundamentals of medicine and surgery are mastered before training is narrowed to and concentrated upon the specialty. Appreciation constantly grows of the necessity of understanding the functioning of the body as a whole before success can be expected in treating any part of it. The day is near when hospitals generally will extend privileges to practice a specialty in their institutions only to those who have had the requisite general and special training to insure competence. Many hospitals already limit privileges in this manner, no longer recognizing the physician who elects to practice surgery, and the surgeon who elects to practice a surgical specialty, without first obtaining the proper training in an approved institution.

The pivotal point in the training program is unquestionably the senior surgeon in the hospital which conducts graduate training in surgery. Upon his conscientious preceptorship the success of any plan will depend. There can be no substitution for the personal interest of the experienced surgeon in the progress of the learner. Hence the ultimate responsibility for the success of postwar graduate training will rest not alone upon hospital administrators and medical associations, but upon the Fellows of the College and other competent surgeons who assume personal responsibility for upholding high standards of training.

Leadership has been wisely exercised by the surgical profession and it is demonstrable that in the critical educational situation which now exists the American College of Surgeons is well prepared by its established program to direct the voluntary efforts of surgeons to apply effective remedies to overcome the losses sustained during the war. The teaching hospital is the essential instrumentality. We shall need many more.

The future of surgery is involved in the preparation for postwar world leadership in the healing arts as now planned and developed by physicians and hospitals in the American countries. The surgeon who helps his hospital to maintain or to inaugurate a program of graduate training in surgery under the wartime difficulties is rendering patriotic, scientific, educational, and humanitarian service, and is helping his profession and his hospital to build a firm foundation for public good will now and after the war.

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